Journal of
CHRONIC
DISEASES

VOLUME 12 . NUMBER 1

JULY, 1960

Medical Genetics 1959

VICTOR A. MCKUSICK, M.D.
BALTIMORE, MD.

From the Division of Medical Genetics, Department of Medicine, Johns Hopkins University School of Medicine, and the Joseph Earle Moore Clinic, Johns Hopkins Hospital

(Received for publication March 2, 1960)

WITH THE COLLABORATION OF

HELEN ABBEY
R. M. BANNERMAN
E. J. BATTERSBY
N. O. BORHANI
S. H. BOYER, IV
A. A. BUCK
B. H. COHEN
J. R. ESTERLY
N. B. ESTERLY
D. A. PRICE EVANS
M. A. FERGUSON-SMITH
F. R. FRANKE
H. GORDON
M. R. HAWKINS
J. S. HUTCHESON
A. W. JOHNSTON
J. T. LEEMING
J. M. LEVITSKY
A. M. LILIENFELD
A. B. MCKUSICK
K. A. MANLEY
C. F. MERRYMAN
I. H. PORTER
A. L. PUSCH
A. P. SKYRING
SOON KYU SUH
RALPH WEBER
W. J. YOUNG

DRS. CURT STERN of Berkeley, California, HARRY HARRIS of London, and JAMES H. RENWICK of London and Glasgow contributed during stays of from one to a few months in duration. DR. BARTON CHILDS read the manuscript and provided useful suggestions.

OUTLINE*

I. New Books, Journals, Symposia, and Congresses
II. History
III. General Genetics, Selected Reports
IV. Human and Medical Genetics, General Considerations
V. Methods
VI. Cytogenetics in Man
VII. Biochemical Genetics
VIII. Congenital Malformations
IX. Alimentary Tract, Including Pancreas, Biliary Tract, and Liver
X. Blood and Hematopoietic System
XI. Cardiovascular System
XII. Connective Tissue
XIII. Ear
XIV. Endocrine System
XV. Eye
XVI. Genital System
XVII. Muscle
XVIII. Neoplasms
XIX. Nervous System
XX. Skeletal System
XXI. Skin and Other Integumental Structures
XXII. Teeth
XXIII. Urinary System
XXIV. Miscellaneous

*Addition of a separate chapter on "Cytogenetics in Man" has been indicated by the important developments in this field during 1959. Otherwise, the organization is as in "Medical Genetics 1958." Sections referred to by paragraph numbers 1 through 293 are those in "Medical Genetics 1958" (J. CHRON. DIS. 10:255-363, 1959); paragraph numbers 294 through 643 indicate sections in this issue.

VOL 12 196

I. NEW BOOKS, SYMPOSIA, AND CONGRESSES

Books.—

294. Anfinsen, C. F.: The Molecular Basis of Evolution, New York, 1959, John Wiley & Sons, Inc.

This highly recommendable book, written from the point of view of a biochemist at the National Heart Institute, covers those problems of genetics in which biochemical analysis has been most successful in recent years: the functional, structural, and chemical properties of the genetic material, structure and biosynthesis of nucleic acids, protein structure, and biosynthesis. The experiments on which our current understanding of these matters are based are described and references to the original publications are provided. Both geneticists and biochemists should be grateful to the author for the finished product. The topics covered are similar to those in Zamenhof's book (see ¶315); we are fortunate to have two such valuable presentations of the basic biochemistry of inheritance. Anfinsen's monograph is broader in its scope and somewhat more comprehensive in its discussions.

OL.
12
960

295. Burnet, Sir Macfarlane: The Selection Theory of Immunity, London, 1959, Cambridge University Press.

Also, The Clonal Selection Theory of Acquired Immunity (The Abraham Flexner Lecture, 1958), Nashville, 1959, Vanderbilt University Press.

The clonal selection theory is concerned with the way in which cell populations are altered in the presence of antigens. The immunologic success of a cell and its descendent clone is measured by the antibodies which it can produce. The theory is a neo-Darwinian one which demands that "immunological specificity is based on a special type of differentiation occurring in embryonic life plus a subsequent high potential for somatic mutation." The hypothesis, which is of enormous importance to medicine, rests upon incompletely proved tenets; the challenge for proof and the clarity of writing render this work one of the most important of the decade.

296. Cold Spring Harbor Symposia on Quantitative Biology, vol. XIII, Exchange of Genetic Material: Mechanisms and Consequences, Cold Spring Harbor, N. Y., 1959, Biological Laboratory.

As Demerec points out in the foreword, "The problem of genetic recombination was broadly interpreted by the organizers of this Symposium to include processes involved in the synthesis of genetic materials, processes of recombination within gene loci and between closely linked loci, classical crossing over in Drosophila, consequences of recombination within populations, and the effect of recombination on gene stability."

This volume comprises the proceedings of the symposium held in June, 1958, and includes thirty-six contributions distributed in the following seven major sections:

Replication and recombination of genetic material

Recombination of genetic material

Studies of crossing over and segregation
Recombination and gene interaction
Recombination within populations
Recombination and breeding systems
Recombination and gene stability

The contributions range from replication of DNA through lysogenesis, transduction, paramutation, transformation, and nucleocytoplasmic recombinations to inversion heterozygosity in populations and include studies on Drosophila, maize, Salmonella, Aspergillus, Neurospora, yeast, phage, and *Diplococcus pneumoniae*. One cannot merely browse through this book; careful study and fairly advanced knowledge are required. As is the case with the other volumes of this series, it will serve as an excellent review and reference work in this area of genetics, one which is currently enjoying a high level of interest and productivity.

VOL. 12 1960

297. Dunn, L. C.: Heredity and Evolution in Human Populations, Cambridge, Mass., 1959, Harvard University Press.

This is a genetic interpretation of evolution and anthropology written for the intelligent layman. Variation and its genetic basis, the principles of population genetics, race formation, and isolates are discussed.

298. Dupree, A. H.: Asa Gray, 1810-1888, Cambridge, Mass., 1959, Belknap Press of Harvard University Press.

This readable biography is timely because Asa Gray, the Harvard botanist, was one of the early protagonists of Darwinism. He provided Darwin with information valuable to the latter's theory. Some of the more interesting parts of this biography concern the Darwin-Gray relationship and Gray's controversy with Agassiz over the Darwinian theory.

299. Glass, B., Temkin, O., and Straus, W. L., Jr., editors: Forerunners of Darwin, 1745-1859, Baltimore, 1959, Johns Hopkins Press.

One of the most interesting of this series of essays is Glass's concerning Maupertius (1698-1759). "Here was a man who argued on genetic grounds against preformation . . .; who investigated human heredity in a manner calculated to draw the admiration of any geneticist of the present day, and who applied mathematical theory of probability to genetics over a century before Mendel; who undertook experiments in animal breeding to throw light on his theories; who formulated a theory of heredity that was particulate and involved the mutual attraction of analogous particles provided by each parent, and that implied segregation, dominance, and independent assortment; and finally, who formed a theory of organic evolution based upon mutation, natural selection, and geographical isolation." His pedigree of polydactyly, which demonstrated inheritance sometimes from the father, sometimes from the mother, is one of the earliest to be found.

The largest single contributor to the volume is Arthur O. Lovejoy, formerly professor of philosophy at Johns Hopkins University. Several of Lovejoy's papers on the development of evolutionary thought are reprinted.

300. Hammons, Helen G., editor: Heredity Counseling, A Symposium sponsored by the American Eugenics Society, held in December, 1957, New York, 1959, Paul B. Hoeber, Inc.

Contributors included Dice, Falls, Fraser, Glass, Herndon, Kallmann, McKusick, Neel, Oliver, Reed, Schull, Warkany, and Witkop.

301. Harris, H.: Human Biochemical Genetics, London, 1959, Cambridge University Press.

Harris' scholarly opus covers the subject of biochemical genetics in considerable depth. It is carefully prepared and has a firm base in the author's own numerous contributions to the field. It is a major contribution. The organization is as follows:

Introduction, including the concept of inborn errors of metabolism
Some aspects of Mendelian heredity in man
Amino acid metabolism
Carbohydrate metabolism
Human hemoglobins
Blood group substances
Plasma proteins
Other inherited disorders of metabolism (porphyria, methemoglobinemia, hyperbilirubinemia, acatalasemia, vitamin D–resistant rickets, hypophosphatasia, diabetes insipidus, hemochromatosis, hyperoxaluria, and gout)
The problem of gene action

302. Hsia, D. Y.-Y.: Inborn Errors of Metabolism, Chicago, 1959, Year Book Publishers, Inc.

This book will have usefulness as a catalog of disorders of biochemical genetics in man. A list of procedures used in the chemical study is given in the appendix.

There are a number of inaccuracies and categoric statements which may not be true. Dominant and recessive forms of alkaptonuria are referred to without qualification (pp. 18 and 114). Knox's review is not listed. The suspicion that the "dominant" pedigrees result from marriage of affected homozygotes with normal heterozygotes should have been mentioned. Also in connection with alkaptonuria, it is stated that when inherited as a recessive trait, "1 out of 4 children will be affected" (p. 114). Some mention should be made of the fact that ascertainment in human material is by necessity through an affected individual and that 25 per cent is not the proportion affected found for recessive traits under these circumstances. It is stated that ". . . the genes for thalassemia and sickle cell anemia are located on different chromosomes" (p. 59). It is dogmatically stated that "resistant rickets represents a congenital defect in the renal transport

mechanism for phosphorus" (p. 215). Winter and colleagues, who were quoted, are themselves more cautious in interpretation of the defect; there is some reason to think the primary defect is not in the kidney. The term "lipochondrodystrophy" is used repeatedly for gargoylism, or the Hurler syndrome (p. 251 ff.). It is unfortunate to perpetuate this designation based on a mistaken view of the nature of the inclusion material. Gargoylism is listed among the disorders of lipid metabolism. On the other hand, the author states that gargoylism "is a generalized disease process characterized by defects in the construction of the *collagenous* tissues within the body." If the author had said "connective tissues," we would have no quarrel. There is a deplorable tendency to use "collagenous tissue" synonymously with "connective tissue" in much contemporary writing, e.g., "collagen disease" and "collagen-vascular disease." In the table of "conditions which *may* be genetically determined" (p. 286), several conditions—acatalasia, angioneurotic edema, Milroy's disease, Laurence-Moon-Biedl syndrome, primary amyloidosis, PTC tasting—would seem to deserve kinder treatment than relegation to this uncertain group. Methods for identifying heterozygotes in conditions such as phenylketonuria and cystic fibrosis are made to sound more accurate and sensitive than possibly are deserved.

In the rapidly evolving field of medical genetics, it takes a brave author to write a general textbook; it is likely to be proved inaccurate before publication is complete and sections on some areas in which the author has not worked personally are likely to be weak. The author is to be congratulated on his courage and for what is, in general, authoritative coverage.

A few typographic and bibliographic errors have crept in: "succosuria" for "sucrosuria" (p. 286), "neoplasma" for "neoplasms," "elliptocytosis–hemoglobin disease" for "elliptocytosis–hemoglobin C disease" (p. 35), and "spherocytosis–hemoglobin disease" for "spherocytosis–hemoglobin S disease" (p. 54). The pedigree of hemophilia in the descendants of Queen Victoria is not given by Brinkhous in the reference cited.

The title deserves comment: it is obviously not original. Those of us who entertain a certain hero worship for Garrod would, I am sure, never think of using the title. It seems to border on the sacrilegious.

303. Huron, R., and Ruffie, J.: Les methodes en génétique générale et en génétique humaine, Paris, 1959, Masson & Cie.

The mathematical methods of genetics are reviewed after an outline of principles of genetics. H. M. Slatis (Am. J. Human Genet. 11:390, 1959) indicated that the errors are so numerous as to render the book of doubtful usefulness.

304. Kempthorne, O., editor: Biometrical Genetics, New York, 1959, Pergamon Press, Inc.

305. Lamy, M., Royer, P., and Frézal, J.: Maladies héréditaires du métabolisme chez l'enfant, Paris, 1959, Masson & Cie.

After a preface by Robert Debré and a discussion of selected general principles of genetics, the authors give a thorough discussion of galactosemia, the

VOL. 12 196

glycogenoses, phenylketonuria, alkaptonuria, adrenal hyperplasia, cystinuria, renal diabetes, vitamin D–resistant rickets, diabetes insipidus, mucoviscidosis, the sphingolipidoses, gargoylism, spontaneous hypoglycemia, and diabetes mellitus.

306. Montagu, A.: Human Heredity, Cleveland and New York, 1959, World Publishing Company.

This is a moderately long book which covers essentially all aspects of human heredity. The presumed Mendelian inheritance of a large number of "inherited disorders of man" is given as an appendix. Books for additional reading and publications referred to in the text are listed. A possible criticism is that the impression may be conveyed that the inheritance of traits, such as hair form, eye color, and form of the ear lobes, is more straightforward than is indeed the case. Incomplete sex-linkage is discussed in more definite terms than current pedigree or cytologic information would warrant. The nonmedical background of the author leads him into errors, such as the listing of mitral stenosis, along with pseudohypertrophic muscular dystrophy and color blindness, as a trait dependent on a sex-linked gene (p. 182).

307. Osborne, R. H., and DeGeorge, F. V.: Genetic Basis of Morphological Variation. An Evaluation and Application of the Twin Study Method, Cambridge, Mass., 1959, Harvard University Press (Commonwealth Fund).

The twin study reported here is that which also produced data on the factor of heredity in the determination of level of serum cholesterol (¶'s 167, 407), erythrocyte sedimentation rate (¶369), dimensions of the anterior permanent teeth (¶273), and susceptibility to dental caries (¶273). Reference is made to studies of the electrocardiogram and ballistocardiogram from the same point of view; these results should be of considerable interest. The monograph above confines itself to methodologic and somatologic aspects. Provided are critiques of the twin method and of quantitative inheritance. They point out an interesting pitfall of the twin method, namely, that there may be a large discrepancy between the index of heritability derived from twin studies and that based on studies of familial aggregation. A prime example is Mongolism, for which monozygotic twins are almost always concordant and dizygotic twins almost always discordant; yet familial aggregation for Mongolism is not impressive. Obtaining a twin sample and diagnosing zygosity are discussed. The studies failed to demonstrate any strong influence of heredity in the determination of body weight, head length, and certain measurements taken transversally to the long axis, in *adults.*

308. Peckham, M., editor: The Origin of Species by Charles Darwin, Philadelphia, 1959, University of Pennsylvania Press.

309. Penrose, L. D.: Outline of Human Genetics, London, 1959, William Heinemann, Ltd.

Like Fraser Roberts' book (¶311), Penrose's is one that can be recommended to those who are seeking quick information on human genetics. Penrose has a rare ability to present information in a lucid manner without sacrificing accuracy.

The organization is as follows:

Basic considerations (Interesting historical facts are presented among other information; a seldom-seen portrait of Weinberg is included.)
Single-gene effects
Genes and populations
Association and linkage
Interplay of environment and heredity (Twins, congenital malformation, and other topics are discussed.)
Eugenics and dysgenics

310. Peters, J. A., editor: Classic Papers in Genetics, New York, 1959, Prentice-Hall, Inc.

James A. Peters of San Fernando Valley State College edited this paperback volume of twenty-eight *Classic Papers in Genetics.* The following were included:

a. Mendel, G.: Experiments in Plant-Hybridization, Verhandl. naturh.-med. Ver. in Brunn, Abhandlungen, vol. IV., 1865 (appeared in 1866).

b. Johannsen, W.: Heredity in Populations and Pure Lines. A Contribution to the Solution of the Outstanding Questions in Selection, *in* Ueber Erblichkeit in Populationen und in reinen Linien, Jena, 1903, VEB Gustav Fischer Verlag.

c. Sutton, W. S.: The Chromosomes in Heredity, Biol. Bull. 4:231, 1903.

The concept that the hereditary particles are borne by the chromosomes (the Sutton-Boveri hypothesis) is developed in a closely reasoned analysis. "Thus the phenomena of germ-cell division and of heredity are seen to have the same essential features, viz., purity of units (chromosomes, characters) and the independent transmission of same." Sutton was then 26 years old.

Walter Stanborough Sutton (1877-1916) later studied medicine; he was graduated from Columbia University College of Physicians and Surgeons in 1907. He was a practicing surgeon in Kansas City, Missouri, until his untimely death after an operation for appendicitis.

d. Bateson, W., and Punnett, R. C.: Experimental Studies in the Physiology of Heredity. Reports of the Evolution Committee, Royal Society, Reports Nos. 2, 3, and 4, 1905-1908.

e. Hardy, G. H.: Mendelian Proportions in a Mixed Population, Science 28:49, 1908.

". . . I should have expected the simple point which I wish to make to have been familiar to biologists. However, some remarks of Mr. Udny Yule, to which Mr. R. C. Punnett has called my attention, suggest that it may still be worth making. In the *Proceedings of the Royal Society of Medicine* (Vol. 1, p. 165) Mr. Yule is reported to have suggested, as a criticism of the Mendelian position, that if brachydactyly is dominant 'in the course of time one would expect, in the absence of counteracting factors, to get three brachydactylous persons to one normal.' It is not difficult to prove, however, that such an expectation would be quite groundless." Hardy proceeds to "prove" what is now called the Hardy-Weinberg law—that genotype frequencies remain constant in the population

from generation to generation, assuming random mating, uniform fertility, and so on. He points out that Karl Pearson appreciated this fact (Phil. Tr. Roy. Soc. (A) 203:60).

Godfrey Harold Hardy (1877-1947) is described by C. P. Snow (*The Two Cultures and the Scientific Revolution, 1959*) as "one of the most distinguished pure mathematicians of his time, and a picturesque figure in Cambridge both as a young don and on his return in 1931 to the Sadleirian Chair of Mathematics." For Hardy's portrait, see *Mathematical Gazette*, 1948.

f. Morgan, T. H.: Sex Limited Inheritance in Drosophila, Science 32:120, 1910.

We would now call this sex-linked inheritance, reserving the term "sex-limited" for a trait which occurs only in one sex. This important work developed from the discovery of a white-eye mutant in the fruit fly.

OL.
12
960

g. Sturtevant, A. H.: The Linear Arrangement of Six Sex-Linked Factors in Drosophila, as Shown by Their Mode of Association, J. Exper. Zool. 14:43, 1913.

Mapping of the sex chromosome was performed by observing the frequency of crossovers (recombinants) in the progeny of fruit flies with two sex-linked traits. The unit of "distance" on the chromosome was taken as the percentage of crossovers observed in the progeny.

h. Wright, S.: Color Inheritance in Mammals, J. Hered. 8:224, 1917.

This was an early contribution to physiologic genetics. Previously, little attention had been paid to the pathways between the gene and its observed expression.

i. Dunn, L. C.: Unit Character Variation in Rodents, J. Mammal. 2:125, 1921.

j. Muller, H. J.: Variation Due to Change in the Individual Gene, Am. Naturalist 56:32, 1922.

k. Bridges, C. B.: Sex in Relation to Chromosomes and Genes, Am. Naturalist 59:127, 1925.

This important paper presented evidence, mainly from Drosophila, in support of the theory that sex determination is a matter of balance between the masculinizing influence of the autosomes and the sex chromosome, specifically the X chromosomes. In 1959 it was demonstrated that in man and mouse this is not the mechanism of sex determination (¶388).

l. Sturtevant, A. H.: The Effects of Unequal Crossing Over at the Bar Locus in Drosophila, Genetic 10:117, 1925.

The "position effect" was described and so termed.

m. Muller, H. J.: Artificial Transmutation of the Gene, Science 66:84, 1927.

The mutagenic effect of x-ray was described.

n. Creighton, H. B., and McClintock, B.: A Correlation of Cytological and Genetical Crossing-over in Zea Mays, Proc. Nat. Acad. Sc. 17:492, 1931.

o. Painter, T. S.: A New Method for the Study of Chromosome Rearrangements and Plotting of Chromosome Maps, Science 78:585, 1933.

p. Bridges, C. B.: The Bar "Gene," a Duplication, Science 83:210, 1936.

q. Beadle, G. W., and Tatum, E. L.: Genetic Control of Biochemical Reactions, Proc. Nat. Acad. Sc. 27:499, 1941.

r. Avery, O. T., MacLeod, C. M., and McCarty, M.: Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types, J. Exper. Med. 79:137, 1944.

The transforming substance was shown to be DNA.

s. Lederberg, J., and Tatum, E. L.: Gene Recombination in Escherichia Coli, Nature, London 158:558, 1946.

By demonstrating recombination in mixed cultures of bacteria with multiple nutritional mutants, the authors provided strong evidence for a sexual process in *E. coli.*

t. Genetics Conference, Committee on Atomic Casualties, National Research Council: Genetic Effects of the Atomic Bombs in Hiroshima and Nagasaki, Science 106:331, 1947.

u. McClintock, B.: The Origin and Behavior of Mutable Loci in Maize, Proc. Nat. Acad. Sc. 36:344, 1950.

v. Horowitz, N. H., and Leupold, U.: Some Recent Studies Bearing on the One Gene–One Enzyme Hypothesis, Cold Spring Harbor Symp. Quant. Biol. 16:65, 1951.

w. Zinder, N. D., and Lederberg, J.: Genetic Exchange in Salmonella, J. Bact. 64:679, 1952.

Transduction was described.

x. Watson, J. D., and Crick, F. H. C.: Molecular Structure of Nucleic Acids, Nature, London 171:737, 1953.

The now familiar Watson-Crick model was described.

y. Stadler, L. J.: The Gene, Science 120:811, 1954.

z. Sturtevant, A. H.: Social Implications of the Genetics of Man, Science 120:405, 1954.

aa. Fraenkel-Conrat, H., and Williams, R. C.: Reconstitution of Active Tobacco Mosaic Virus From Its Inactive Protein and Nucleic Acid Components, Proc. Nat. Acad. Sc. 41:690, 1955.

bb. Benzer, S.: Fine Structure of a Genetic Region in Bacteriophage, Proc. Nat. Acad. Sc. 41:344, 1955.

311. Roberts, J. A. Fraser: An Introduction to Medical Genetics, London, 1959, Oxford University Press.

Fraser Roberts' book is probably, as he indicates in the preface, unique (in the English language) in its presentation of medical genetics exclusively in terms of man and human disease. Examples from other forms of life are excluded. The treatment is made as nonmathematical as possible. Lamy of Paris has prepared a comparable text in French.

The author should be given a hearty vote of thanks for providing an answer to the frequently recurring question from clinicians and medical students with lukewarm interest, "Where can I read up on medical genetics?" The book is not, and is not intended to be, suitable as more than an introduction for the serious student of human heredity.

VOL. 12 196

Still there is much that the serious student will learn from this master at the teaching, research, and clinical practice of medical genetics. The choice of illustrative pedigrees for various modes of inheritance is, in many instances, interesting. Keratosis follicularis (Darier's disease) is presented as an example of a sex-linked dominant or intermediate characteristic (p. 99). The pedigree of microphthalmia is an interesting example of sex-linked recessive inheritance (Fig. 45); the affected males do not live to reproduce. Komai's pedigree of cataract (Fig. 18) is an interesting possible example of the homozygous state of a "dominant" gene. The author makes the following three-way division of hereditary traits (which although distinctly arbitrary may be a useful way to think about genetic disease): (1) major harmful (and usually relatively rare) genes, (2) polymorphic traits, mostly "normal," and (3) polygenic, or multifactorial, traits. The recent cytogenetic information on the Turner and Klinefelter syndromes and on sex determination in man is included as an addendum, but the new information on Mongolism is not included. The blood groups are particularly well discussed, and properly so in a textbook intended for general medical consumption. The author points out (p. 124) that progress with reference to the Kell blood group system is rather typical. In 1946 an antiserum was discovered which reacted positively with roughly 10 per cent of randomly selected blood (Kell positive). Three years later a new antiserum was discovered and given the name "Cellano" for the woman who developed it as a result of fetomaternal incompatibility. The Cellano gene was found to be allelomorphic with respect to the Kell gene. Both alleles determine the presence of an antigen capable of producing a corresponding antibody. There is, therefore, no dominant-recessive relationship as might have been claimed before Cellano was identified. In discussing the genetics of common disorders, the author makes the useful point that in any large diagnostic category one can pick out one or more instances of single major gene determination. The examples cited are (1) in cancer of the colon, familial polyposis, (2) in cancer of the esophagus, tylosis, and (3) sinus infection in a striking family reported by Grüneberg. Such families, when included in large series collected for estimates of empirical risk, exaggerate the risk for the entire group; on the other hand, the risk calculated from the whole series is too low for these unusual families.

One can find fault with a few details: (1) Pieter's pedigree of alkaptonuria (Presse méd., 1925) which suggests dominant inheritance is included as a prime example of this mode of inheritance, despite the penetrating analysis of Eugene Knox (¶95) which concludes that marriage of homozygotes with heterozygotes through consanguinity and isolation could account for the minority of pedigrees showing this pattern. (The recent work of Milch restudying the same kindred [¶394] makes Knox's conclusion very likely.) (2) As an example of mutation, Keeler's piebald Negro family (1933), descendant from a woman born in Louisiana in 1853, is cited. The woman was the only affected child out of 9 offspring from putative parents who were normal. The probability of illegitimacy in this situation is much greater than the probability of mutation. (3) The author states, "At present, therefore, it is not necessary to assume that there is more than one gene for elliptocytosis" (p. 147). Most interpret the linkage data as indicative of

two types—one linked to Rh genes and one not linked (Lawler and Renwick). (4) In connection with gargoylism the author states, "It is believed to be essentially a disorder of lipoid metabolism" (p. 175). Although many still hold this "belief," the better recent evidence on the nature of the basic defect (¶'s 181, 522) should have been cited. (5) It is stated, "Ordinary major genes are confined to the euchromatin. Polygenes occur in the heterochromatin, though they may occur in the euchromatin as well" (p. 201). There is some evidence to suggest that this statement is correct (see Kenneth Mather's *Biometrical Genetics: The Study of Continuous Variation*, 1949, pp. 19-22). Information is so limited, however, that it would seem best to have avoided mention in this elementary text.

312. Sheppard, P. M.: Natural Selection and Heredity, New York, 1959, Philosophical Library, Inc.

The author, professor of genetics at the University of Liverpool, has reviewed the mechanisms of evolution in the light of modern genetics. Like several other books referred to in this section (¶'s 298, 299, 308), this one is a logical acknowledgment of the century which has passed since the Darwin-Wallace papers were read to the Linnean Society of London (July 1, 1858) and Darwin's *The Origin of Species* (1859) was published. The topics covered include the following: natural selection, simple Mendelian inheritance, some other Mendelian principles, polymorphism, polygenic inheritance, mutation, genetic drift, protective coloration, and others.

313. von Verschuer, O.: Genetik des Menschen. Lehrbuch der Humangenetik, Munich and Berlin, 1959, Urban & Schwarzenberg.

This is a textbook which, as one reviewer states, is in the tradition of Baur-Fischer-Lenz. It will probably be a useful source to German-speaking workers in the field of human genetics. In his tabulations of hereditary diseases, the author was able to enumerate 374 autosomal and thirty-eight sex-linked loci as responsible.

314. Wallace, B., and Dobzhansky, T.: Radiation, Genes, and Man, New York, 1959, Henry Holt & Company, Inc.

Not all readers will agree with the closing sentences of this book; nevertheless, in light of the excellent presentation preceding them, they deserve careful consideration: "All biological species have evolved; but only man knows that he has evolved. The evolution of all life in the past has been controlled by natural selection. It now seems that man neither can nor need rely on natural selection alone; the genetic effects of radiation are in part responsible for this change. For natural selection, man must substitute a conscious direction based on knowledge. The requisite knowledge will soon be forthcoming; let us hope that wisdom lags not too far behind."

The book is not solely designed for the professional biologist; still, human biologists and, in fact, every individual concerned with the effects of radiation on the human population cannot fail to profit by reading it carefully. It is not

VOL. 12 196

all easy reading; a rather high level of sophistication is achieved in the closing chapters, but the reader has been amply prepared by the earlier sections to understand and appreciate the discussion of the effects of radiation on populations. It is highly recommended as a very lucid and valuable presentation of this critical topic. The table of contents follows:

Atomic energy—friend or foe?
Heredity, environment, genes, and chromosomes
Spontaneous mutation
Atoms and radiations
Induction of mutation by radiation
Genes in mendelian populations
Genetic effects of radiation on populations
Some unsolved problems
Concluding survey

DL.
12
960

315. Zamenhof, S.: The Chemistry of Heredity, Springfield, Ill., 1959, Charles C Thomas, Publisher.

The author, associate professor of biochemistry at the Columbia University College of Physicians and Surgeons, has well earned hearty congratulations and thanks for an authoritative, lucid, up-to-the-year (March, 1959) review of chemical mechanisms in heredity. Essentially the same ground is covered as in the McCollum-Pratt Symposium, "The Chemical Basis of Heredity" (1957). In 83 pages of text the author discusses the chemical nature of the genes, which he prefers to call "hereditary determinants," the intermediary system or messenger between genes and cytoplasmic reactions, and the peripheral reactions, that is, the chemical processes in the cytoplasm under gene control. The chemical nature of mutation is discussed with the genes, and hereditary defects in man are briefly surveyed in illustration of the manner in which gene action is becoming increasingly susceptible to chemical interpretation. A list of 185 references increases greatly the usefulness of the review without interfering with the smooth flow of a fascinating, stranger-than-science-fiction story.

316. Zirkle, R. E., editor: A Symposium on Molecular Biology, Chicago, 1959, University of Chicago Press.

A majority of the twenty-two contributions are of genetic interest: for example, Sinsheimer, on the structure of DNA; Kornberg, on enzymatic synthesis of DNA; Rich, on the relationship between DNA and RNA; Anfinsen, on protein structure and biologic activity; Swift, on nucleolar function; Taylor, on autoradiographic studies of the organization and mode of replication of chromosomes; and Zirkle, on the structure of the mitotic spindle.

A New Journal.—

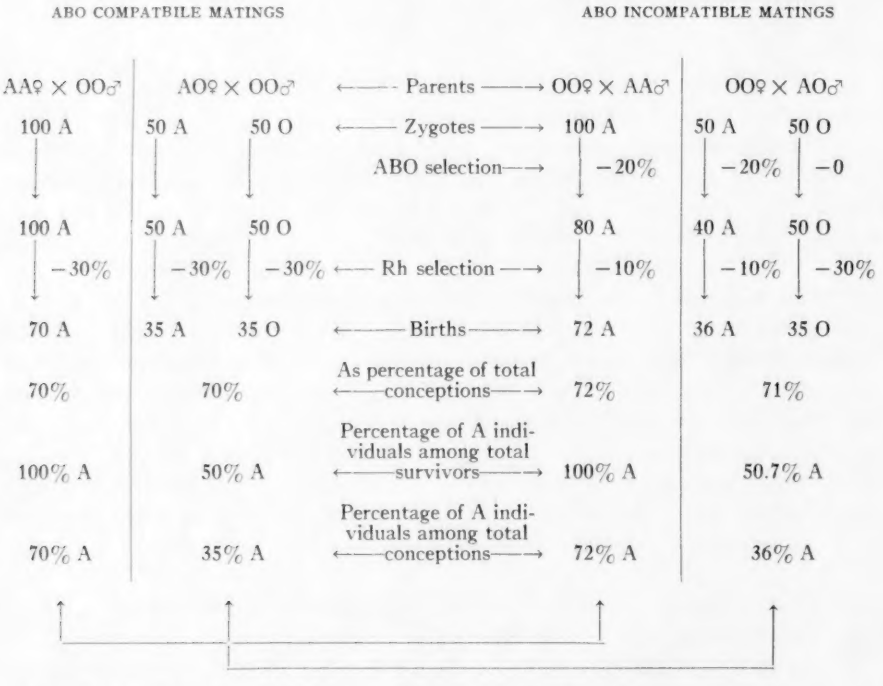
317. A new periodical, the *Journal of Molecular Biology*, published by Academic Press, Inc., with J. C. Kendrew of Cambridge University as editor, first appeared in 1959. It will undoubtedly present a considerable number of papers of genetic interest.

Symposia.—

318. The symposium held in April, 1958, at the University of Wisconsin in connection with the establishment of the Department of Medical Genetics in the School of Medicine (¶23) was published in the *Journal of Medical Education* (April, 1959) and in the *American Journal of Human Genetics* (June, 1959).

Stern reviewed studies of the human chromosomes. Steinberg (see ¶372) provided a commendable survey of statistical methods in human genetics, starting with pedigree analysis and going on to segregation analysis, estimation

TABLE I. SELECTION PRESSURES IN RH AND ABO INCOMPATIBLE MATINGS—A HYPOTHETIC EXAMPLE



Negative selection against ABO incompatible zygotes—20 per cent.

Negative selection against Rh incompatible zygotes with ABO incompatibility—10 per cent; with ABO compatibility—30 per cent.

Modified from Cohen, B. H., and Glass, B.: J. M. Educ. 34:414, 1959.

of gene frequency, and mutation rates. It was, of course, impossible to cover all aspects of human genetics for which statistical methods have been developed. Linkage and much of population genetics were not discussed.

It is the philosophy of the Wisconsin department that bacterial and virus genetics is a bona fide part of the purview of a department of genetics in a medical school. Reflecting this philosophy, Koprowski discussed virus genetics and Stocker

VOL. 12 1960

bacterial genetics. Both leave the reader with no doubt of the importance of the genetic characteristics of the infecting agent to such clinically important matters as the carrier state, immunization, sensitivity to antibiotics, and virulence. Owen discussed genetic aspects of tissue transplantation. Graham discussed problems on the inheritance and mechanism of "vascular hemophilia"—a disorder or class of disorders in which there is both a defect in antihemophilic globulin and in capillary integrity. Boyd found red blood cell antigen B in American Indian mummies which may be more than 8,000 years old. The Mongoloid ancestors of the American Indians are thought to have crossed the Bering Strait from Asia some 20,000 to 25,000 years ago. In Asia the blood group B gene is frequent. In the American Indian it is almost nonexistent. Boyd suggests that early American Indians had a frequency of the B gene closer to that of their Asian relatives but that in this hemisphere a strong selection against blood group B reduced its frequency from values in the vicinity of 0.30 to zero. That blood groups are not selectively neutral may be illustrated by these findings, and one of the few stumbling blocks to the theory of Asian origin of the American Indian is removed.

DL.
2
960

TABLE II. CRITERIA FOR RECOGNITION OF SELECTION IN ABO BLOOD GROUPS AT DIFFERENT STAGES*

STAGE	EFFECT OBSERVED IN
Fertilization	Fertility of parent; sex ratio of children
Intrauterine	Spontaneous abortions
Perinatal	Stillbirths; hemolytic disease
Postnatal and adult	Resistance or susceptibility to diseases; longevity

From Matsunaga, E.: Jap. J. Human Genet. 4:173, 1959.
*Matsunaga presented some evidence bearing on each.

Clarke discussed associations of blood groups with some specific diseases, especially peptic ulcer. The data of Evans are quoted to suggest that quantitative differences in mucoid substances in gastrointestinal secretions cannot account for the increased frequency of peptic ulcers in type O individuals and nonsecretors.

Matsunaga and also Cohen and Glass spoke on the general subject of selection and blood group incompatibility (see Tables I and II).

319. The Upstate Medical Center of the State University of New York sponsored a symposium on "Molecular Genetics and Human Disease," held in Syracuse, April 23 and 24, 1959. The symposium will be published in 1960.

320. A Ciba Foundation Symposium on "Biochemistry of Human Genetics" held in Naples during May, 1959, was published with creditable expedition (London, December, 1959, J. & A. Churchill, Ltd.). The contributions were as follows:

a. Penrose, L. S.: Genetical Analysis in Man.

This is an excellent survey of current research in human genetics and of promising areas for future research. "At the present time the application of mathematical methods is no longer a dominating factor. Biochemical methods are now in the ascendant."

b. Kalckar, H. M.: Biochemical Genetics as Illustrated by Hereditary Galactosemia.

Both human and bacterial galactose mutants were discussed. Kalckar mentioned the possibility that many of the manifestations of hereditary galactosemia are the result of inhibition of phosphoglucomutase by galactose-1-phosphate.

c. Kalow, W.: Cholinesterase Types.

On starch gel electrophoresis, differences in mobility of normal and atypical cholinesterase could be demonstrated when decamethonium, which attaches selectively to normal cholinesterase, was added to the serum.

d. Kalmus, H.: Genetical Variation and Sense Perception.

Discussion was limited to congenital stationary night blindness, protanopia, and taste blindness. "There are indications that it may soon be possible to explain some of these deficiencies by comparatively minor alterations of certain macromolecules which are part of the fine structure of the receptors concerned."

e. Childs, B., and Zinkham, W. H.: The Genetics of Primaquine Sensitivity of the Erythrocytes.

Drug-induced hemolytic anemia, favism, and congenital nonspherocytic hemolytic anemia were discussed as three syndromes related to a deficiency of glucose-6-phosphate dehydrogenase in the erythrocyte. The existence of several other derangements of enzyme function was indicated. In the discussion the fact that the heterozygous female has a lower glucose-6-phosphate dehydrogenase enzyme level than the normal hemizygous male was underscored. This fact may be evidence that the defect in glucose-6-phosphate dehydrogenase is not the primary one. Siniscalco thinks there is an element of sensitization involved in favism. He also indicated that the sex ratio of favism varies with age, being about 10 to 1 male preponderance in childhood and 1 to 2 female preponderance in adults. The existence of two forms of the disease—which may be due to different mutants—is suggested by the quantitative difference in glucose-6-phosphate dehydrogenase levels in affected Mediterranean and affected African peoples.

f. Itano, H. A., Singer, S. J., and Robinson, E.: Chemical and Genetical Units of the Haemoglobin Molecule.

g. Hunt, J. A., and Ingram, V. M.: The Genetical Control of Protein structure: The Abnormal Human Haemoglobins.

In the discussion Ceppelini described a new minor hemoglobin component, found by use of the starch block technique and referred to as B_2. The frequency of the trait was estimated as just under one per cent in American Negroes. He had identified 29 carriers in four unrelated families. Ceppelini also presented observations on the 26 offspring from seven matings of sicklemic-thalassemic individuals with normal individuals. With the possible exception of one individual all the offspring had either the sicklemia trait alone (12) or the thalassemia trait alone (13). This suggested that the thalassemia locus is distinct

from but closely linked to the S locus; or, if the one exceptional offspring is either illegitimate or phenotyped incorrectly (there was some suspicion of both possibilities), the thalassemia and sicklemia genes might be allelic. The possibility that the thalassemias are "nonelectrophoretic" amino acid substitutions—an idea expanded by Ingram (¶469)—was mentioned.

h. Rossi-Fanelli, A., Antonini, E., de Marco, C., and Beverecetti, S.: Studies on Foetal Myoglobin.

Differences in the amino acid composition of fetal and adult hemoglobin were described. However, no difference in amino acid composition of fetal and adult myoglobin was demonstrable.

i. Harris, H., Robson, E. B., and Siniscalco, M.: Genetics of the Plasma Protein Variants.

The authors provided a good survey of haptoglobins, transferrins, and other protein variants.

j. Smithies, O., and Connell, G. E.: Biochemical Aspects of the Inherited Variations in Human Serum Haptoglobins and Transferrins.

k. Morgan, W. T. J.: Some Immunochemical Aspects of the Products of the Human Blood Group Genes.

(See ¶'s 491, 504*c*.)

l. Watkins, W. M.: Some Genetical Aspects of the Biosynthesis of Human Blood Group Substances.

(See ¶491.)

m. Ceppelini, R.: Physiological Genetics of Human Blood Factors.

n. Grubb, R.: Hereditary Gamma Globulin Groups in Man.

Polymorphism of the γ globulins in man is demonstrated by agglutination-inhibition reactions. The test system involves (1) Rh-positive red cells coated with, but not agglutinated by, certain incomplete anti-Rh, (2) selected sera from patients with rheumatoid arthritis which are capable of agglutinating these coated red cells, and (3) the serum to be tested. "Positive" sera inhibit the agglutination of (1) by (2). Grubb discussed the possible relationship of Gm type to the pathogenesis of rheumatoid arthritis. Two studies have indicated that in groups of patients with rheumatoid arthritis the distribution of Gm types is what one would expect on the basis of the population from which the cases are drawn. However, data on Gm types in the families of patients with rheumatoid arthritis are necessary. Grubb points out that the frequency of Gm (a+) is nearly 100 per cent in peoples living near the equator and near the poles; furthermore, arthritis is said to be uncommon in residents of the tropics and in Eskimos. However, there is probably no relationship between these two facts. Rheumatoid arthritis is frequent in the American Negro.

Grubb stated that sera with other collagen disorders do not function in place of rheumatoid arthritis sera; however, he has observed the agglutinating capacity in sera from girls with "plasma cell hepatitis."

o. Cavalli-Sforza, L. L., and Coauthors: Panel Discussion on "The Approach by Tissue Culture."

p. Brenner, S.: The Mechanism of Gene Action.

*Congresses.**—

The American Society of Human Genetics met with the American Institute of Biological Sciences at Pennsylvania State University, Aug. 31 to Sept. 2, 1959. The program has been published (Am. Inst. Biol. Sc. Bull. 9:46, 1959). The following are selected reports:

321. Clinical reports. Curth and her colleagues (Columbia University) described hereditary clubbed fingers transmitted as an irregular autosomal dominant characteristic. There was a wide range of severity. In the most severe cases there were periosteal changes of hypertrophic osteoarthropathy.

Fraser (McGill University) described several cases of what appears to be a bona fide new syndrome and which he refers to as Larsen's syndrome, cases of the same disorder having been reported by Larsen, Schottstaedt, and Bost (J. Pediat. 37:574, 1950) under the title, "Multiple Congenital Dislocations Associated With Characteristic Facial Abnormality." The manifestations include multiple dislocation of joints, crooked fingers, dwarfism suggesting achondroplasia in some, micrognathia, cleft palate, ventricular septal defect, anomaly of vertebrae, and peculiar facies with depressed bridge of nose and flat forehead. The disorder appears to be an autosomal recessive characteristic. Expression was quite variable. This is another genetic variety of cleft palate!

McNutt and his colleagues (University of Texas Medical Branch, Galveston) find that the characteristic pes cavus of Friedreich's ataxia can occur in members of the family unaffected neurologically. They raised the question of whether Friedreich's ataxia may be a dominant trait rather than a recessive, as usually thought, or at least whether pes cavus may not be so. Pes cavus may be present at birth or may appear later.

Lynch and his colleagues of the same institution tackled the knotty question of the relationship between Friedreich's ataxia (and other disorders usually placed in the spinocerebellar group, such as Marie's disease and Lévy-Roussy syndrome), Charcot-Marie-Tooth peroneal muscular atrophy, and hereditary spastic paraplegia. They concluded that these are different phenotypic manifestations of the same genotype.

Falls (University of Michigan) described the Hallermann-Streiff syndrome manifested by mandibulofacial dysostosis, congenital mature cataract with the unique property of spontaneous rupture and resorption, microphthalmia, localized alopecia over the sagittal suture related apparently to delayed closure of that suture, dwarfism in some, etc. Although the condition is sufficiently well reproduced from case to case to suggest a consistent genetic basis, none is obvious from the pedigree analyses. Falls suggested that a chromosomal aberration should be sought.

Jackson (Bluffton, Indiana) described two families with hereditary hyperparathyroidism. In one, pancreatitis and, in the other, peptic ulcer occurred

*Much thought was given to the advisability of including this section. It was finally concluded that advantages of early reporting probably outweigh the possible risks of misreporting. If, however, papers presented at meetings were published within the year of review, mention in this section was omitted.

frequently. Jackson thinks this disease is the same as hereditary multiple endocrine adenomatosis, such as was described by Wermer (1954) and by Moldawer, Nardi, and Raker (1954).

322. Genetic transmission in man. Simpson (University of Toronto) studied parents, siblings, and offspring of juvenile diabetics (onset before 20 years of age). Suggestive of autosomal recessive inheritance were (1) the relative frequency of affected children from parent pairs of which both, one, or neither of the parents was affected and (2) the low frequency of affected parents (18/460). She concluded that the same gene is responsible for late as for early onset. She could find no correlation between age of onset in siblings or in parent and child. Toronto is a favorable center for such a study because many of the probands were ascertained in the early 1920's when the advent of insulin attracted them to that city.

Uchida and colleagues (University of Toronto) found an abnormally high sweat electrolyte concentration in *one* parent of many patients with fibrocystic disease of the pancreas and suggested that the disease may be dominant with incomplete penetrance. In families with affected cousins, the common parts of the family were the ones which showed the abnormal sweat test. Uchida pointed out that fibrocystic disease is very rare in Negroes, Chinese, and other inhabitants of hot climates; a strong selection against the gene would be exerted in these areas.

323. Biochemical genetics. Sutton and colleagues (University of Michigan) have found an as yet not fully explored abnormality of urinary excretion of phenolic acids in a patient with myoclonic seizures (mental retardation, seizures, abnormal electroencephalogram [hyparrhythmia of Gibbs], eczema, lack of pigmentation, and familial characteristics).

Chung and Norton (University of Wisconsin) concluded that aldolase is a good early indicator of involvement in the sex-linked Duchenne type of muscular dystrophy; that it is at least as good as, and much more objective than, pseudohypertrophy in identifying this form of the disease. The transaminase level contributes little, in their opinion.

Naylor and her colleagues (Northwestern University) studied glucose-6-phosphate dehydrogenase deficiency in patients with various hemoglobinopathic conditions. No relation, either genetic or clinical, between the two was discovered. Patients with homozygous sickle cell disease had high glucose-6-phosphate dehydrogenase values presumably because of a relatively young red blood cell population.

Price Evans and colleagues (Johns Hopkins University) demonstrated that it is genetically determined whether isoniazid is rapidly or slowly inactivated by the individual. In both Caucasians and American Negroes the proportion of rapid inactivators and slow inactivators is about 50 to 50. Slow inactivation behaves as a homozygous recessive trait.

Hirschhorn (New York University) suggested that there may be at least four types of primary hereditary hyperlipidemia.

324. Other polymorphic traits. In the Conference of Blood Group Workers, Payne, Rolfs, and Hackel (Stanford and Michigan State Universities) described family studies of ten human white cell agglutinins. They derived gene frequencies for the two alleles (+ and −) corresponding to each type and demonstrated satisfactory fit between expected and observed frequencies for matings of various types. Specificially, all offspring of 2 negative parents were without exception negative in the case of each group. Data are insufficient to permit conclusions about interrelationships of the several types, i.e., multiple allelism or linkage.

Steinberg and Giles (Western Reserve University) have discovered a Gm-like factor present in about 28 per cent of American Negroes and in very few Caucasions (see ¶354).

Giblett (University of Washington) presented data on phenotype and gene frequencies for the several haptoglobin and transferrin types. The multiple bands in phenotypes Hp 2-2 and 2-1 are thought to be the result of different levels of aggregation or polymerization of the "2" protein; the "1" protein does not show the phenomenon. In addition to phenotypes Hp 1-1, 2-2, and 2-1, two modified types, 2-1 (mod)^a and 2-1 (mod)^b, are recognized, as well as a presumably hereditary ahaptoglobinemia not explained on the basis of hemolytic disease or severe liver disease. The 2-1 (mod)^a type occurs in about 10 per cent of Negroes. In the 2-1 modified types it appears to be the "2" protein which is atypical. Type 2-1 (mod)^b is also called the "Johnson" type, for the Negro family in which it was first found by Giblett.

Others: 325. Using the double-dichotomy method of sequential analysis for the comparisons, Woolf (University of Utah) found a greater frequency of death from prostatic cancer among the brothers and fathers of probands with the disease than in the control sample.

326. A symposium on cytology in human genetics will be published. Chu (Yale University) described the normal human karyotype. Three methods for obtaining human cells for chromosome study are particularly used: (1) marrow aspiration (Ford), (2) excision of minute piece of skin by cutting off the top of the elevation produced by pulling on a hair (Puck), and (3) cultivation of leukocytes of peripheral blood (Osgood).

Ford (Harwell, England) described aneuploidy in relation to human disorders. Ford referred to unpublished work on the somatic karyotype in 39 Japanese subjects—all had a diploid number of 46. Kodani's finding of 47 and 48 in some must, then, be questioned. It is true that Kodani used germinal tissue. Although a difference from somatic tissue is possible, it seems unlikely. Ford reported that the Y chromosome varies in size in man.

Barr (University of Western Ontario) reviewed the sexual dimorphism found in interphase nuclei, the basis of the now familiar method of "nuclear sexing." Barr has found 10 mentally defective patients with two chromatin masses! Of these, 4 are phenotypic males; and of these 4, 3 have the testicular changes of the Klinefelter syndrome. About 80 per cent of cases of Turner's syndrome are chromatin negative.

Ohno (City of Hope Medical Center, Duarte, California) presented evidence that the sex chromatin is derived from a single X chromosome. Heterochromaticity may be determined by the previous company of the X chromosome; specifically, the heterochromatic chromosome may be that derived from the father. This would be consistent with the report by Kosin and Ishizaki that the female domestic fowl is chromatin positive despite the fact that it is of the heterogametic (ZW) sex in birds. Since there has never been evidence of somatic pairing of chromosomes, the new view of the nature of the sex chromatin is more acceptable.

Sachs and Krim (Weizmann Institute of Science) described studies of a transduction-like phenomenon produced by the polyoma virus in mice. They also reported studies bearing on antigenic markers associated with the Y chromosome.

DeMars (University of Wisconsin) outlined studies of mutation and genetic control of metabolism in cell cultures. Particularly, somatic crossing over might be investigated in cell cultures. Cells from persons heterozygous for the galactosemia gene were proposed as useful subject material. Maintenance of all lines by quick freezing techniques opens up possibilities of study over long periods or at long intervals. Differences in serum requirement, in sensitivity to viruses, in drug resistance, and in other characteristics are now known. Thiamine starvation and some of these other techniques produce morphologic changes in cell cultures which may be useful in recovering the two homozygous cells from cultures of heterozygous galactosemia cells (assuming that somatic crossing over has occurred). A vital staining technique may be useful in such differentiations.

327. Levene (Columbia University) reviewed the subject of association between ABO blood groups and peptic ulcer. He pointed out that the useful measure of association is the cross multiplication method:

If in blood group O those with the ulcer are indicated by a and the controls by c and in other blood groups than O those with the ulcer are signified by b and the controls by d,

$$\frac{ad}{bc} = \frac{a/c}{b/d} = x \text{ (measure of association).}$$

The variable x can go from zero to infinity. When $x = 1$ there is no association.

One can also use y, the natural logarithm of x: $y = \ln x$. The variable y goes from negative infinity to positive infinity, and $y = 0$ represents no association.

$$\text{S.D.}_y = \sqrt{1/a + 1/b + 1/c + 1/d}.$$

One can place upper (x_U) and lower (x_L) confidence limits on x by use of the S.D. value.

An average value for x in studies of peptic ulcer and blood type O is 1.37 i.e., persons with blood type O have on the average a 37 per cent greater risk of peptic ulcer than do persons who are not of this blood type. The x_L and x_U values are 1.31 and 1.44, respectively.

Stratification, early proposed as an explanation of the results, cannot be blamed since similar association has been found in white populations in many

parts of the world. Furthermore, the association has been found in three non-white populations: in the Japanese (Matsunaga), the Chinese (Shanghai, Chinese M. J., 1958), and the American Negro (Buchwalter). Sibling studies done by the Liverpool group fail to show an association. However (and this is a point emphasized by Levene), neither do they disprove it. The x value in siblings was estimated at 1.13, but from the data x_L and x_U were 0.80 and 1.64, respectively. That is, the data are compatible with a true value of x even greater in sibships than that estimated for populations. Levene estimated that to establish the true value of x it would be necessary to have four times as many sibships as in the Liverpool study (N = 425). Levene emphasized the usefulness of determining limits and pointed out the frequent error of concluding that the hypothesis is wrong if the data fail to prove it. The latter was the error implicit in the argument of Manuila (¶157).

VOL. 12 1960

328. Mechanisms of abnormal genetic ratios were discussed in a ½-day program. Examples in Drosophila and maize appear to have a cytologic basis. The example described by Dunn (Columbia University) has a physiologic basis in differential fertilization of eggs according to the haploid genotype of the sperm, i.e., two types of sperm differing with respect to a single locus display different efficiencies of fertilization. Distortions of these types may well occur in man. If so, they would be a potent factor in determining population gene frequencies and in producing non-Mendelian pedigree patterns in man as in other species. Shaw (University of Michigan) analyzed data on aniridia with as complete ascertainment in the Lower Peninsula of Michigan as possible. Only about 42 per cent of children of one affected parent were affected. Because expression of the gene is not variable, lack of penetrance would appear to be inadequate explanation; that is, there were no incomplete mild forms to suggest a "shading off" of phenotype. An explanation in some segregation-distorting mechanism is possible.

Other Events and Items of Note.—

329. Herskowitz (St. Louis University) planned and organized a series of motion pictures of lecture-teaching type covering genetics. The forty-eight ½-hour films in black and white feature three Nobel laureates, Muller, Beadle, and Lederberg, and thirteen other lecturers including Stern, Dunn, Dobzhansky, Watson, Sonneborn, and Crow. Distribution of the films by the McGraw-Hill Book Company, Inc., is scheduled to begin in February, 1960.

330. For a second successive year the Nobel Prize in Medicine and Physiology was awarded to American scientists for contributions to genetics: to Spanish-born Severo Ochoa, aged 54 years, chairman of the Department of Biochemistry, New York University, for discovery of an enzyme in *Acetobacter vinelandii* which promotes production of RNA from smaller organic molecules; and to Arthur Kornberg, aged 41 years, head of the Department of Biochemistry, Stanford University, for discovery of an enzyme in *Escherichia coli* which performs a similar function for DNA. (See Science 130:1099, 1959.)

Lederberg's Nobel lecture, entitled "A View of Genetics," reviewed basic considerations in genetics, including DNA as the carrier of genetic information, genes and viruses, chemical mutagenesis, and the creation of life. A good bibliography is appended to this useful review.

331. As of July 1, 1959, the name of the State Institute for Human Genetics at Uppsala, founded by Gunnar Dahlberg (1893-1956), became the Institute for Medical Genetics of the University of Uppsala. Professor Jan A. Böök is the director.

II. HISTORY

332. Motulsky published his brief scientific biography of Joseph Adams (1756-1818), an English apothecary-physician who wrote two volumes on heredity and disease which displayed considerable insight into problems of medical genetics (see ¶31). The following are quotations from the first of Adams' publications, *A Treatise on the Supposed Hereditary Properties of Diseases*, etc. (1814):

". . . We find the terms *connate* or *congenital*, *hereditary* and *family*, used almost as synonimous [*sic*], and even confounded with *connutrite*, or diseases derived from nurses" (p. 10).

"The distinction between a *family* and *hereditary* peculiarity consists in this; that the first is confined to a single generation, to brothers and sisters, the children of the same parents; and the second is traced from generation to generation" (p. 12). Here Adams appears to recognize the distinction between recessive and dominant traits as to pedigree behavior.

Adams distinguished between hereditary *disposition* and hereditary *predisposition*, in that the former refers to diseases of predominantly genetic determination and the latter to diseases with a significant genetic contribution.

"*Connate* or *congenital* diseases are more commonly family, than hereditary: some of them being mortal, cannot be transmitted . . ." (p. 14).

"*Connate* or *congenital* diseases, it has been remarked, are rarely hereditary, which is the more remarkable, because peculiarities of form in less important parts are often hereditary" (p. 18). Students of congenital malformations would agree in principle with this statement.

". . . The hereditary disposition to elephantiasis is governed by similar laws. In families the most disposed to that disease, such as have the disposition, show it at an early age; and those of the same family, who escape beyond that age, remain free throughout life" (p. 20). Adams had reference almost certainly to families with hereditary lymphedema, definitively described by Milroy almost 80 years later. Unfortunately, later discussion reveals confusion with filariasis.

"I knew three brothers attacked with *angina pectoris*, each as he arrived at the age of about eighteen; to all it proved fatal in a few months; such of the children as grew up to manhood escaped the disease" (p. 20).

Adams insisted that in gout and in madness the hereditary susceptibility is a predisposition, not disposition, and that for this reason much more can be expected from preventive measures. "If the predisposition only is hereditary, the disease may be prevented."

"I know a family in which three brothers were each, in succession, attacked with symptoms of angina pectoris between the age of forty-seven and fifty. The disease was less violent than in the young subjects before mentioned, so that each lived with a continuance of the complaint to a fair old age" (p. 28). Adams considered the susceptibility to angina pectoris here a predisposition not a disposition, with possibilities for preventive measures.

The ill-effects of consanguinity were recognized. "Sir John Sebright informs us, that if a flock of sheep, in which there is a defect, are permitted to breed *in and in*, the defect will gradually increase among them; and Colonel Humphries, by selecting for breeding a marked variety, has succeeded in procuring a flock, all of them with deformed bones" (pp. 33-34).

A remarkable feature of Adams' books is the dearth of speculative material. So often when one reviews publications from this (and other!) periods it is found that the author has permitted himself to be carried in flights of fancy far beyond the point where his observations justify the conclusions.

VOL. 12 196

333. In commemoration of the centenary of the publication of *The Origin of Species* (1859) by Darwin, numerous biographic, historical, and interpretive publications appeared. In *Darwin—Down House—Dawn*, Benjamin Spector provided biographic details, a description of Down House in its original and present states, and finally a précis of the impact of Darwin on intellectual activity in the last century.

Darwin's chronic illness came up for discussion. Most held that it was psychogenic (Alvarez). Adler suggested in was Chagas' disease. He quoted *Journal of the Voyage of H.M.S. Beagle*, in which Darwin described his heavy exposure to *Triatoma infestans*, the vector of *Trypanosoma cruzi*, in a heavily endemic area of Argentina. Gaylord Simpson (Scient. Am., August, 1958) had suggested that the illness was chronic brucellosis. Adler concluded that "his symptoms can be fitted into the framework of Chagas's disease at least as well as into any psychogenic theory of their origin."

III. GENERAL GENETICS, SELECTED REPORTS

Space permits inclusion of relatively few of the many important contributions in the realm of general genetics. Obviously, too, the reviewers cannot claim complete clairvoyance in selecting work that will be pertinent to human genetics. The work reviewed here, however, seemed of particular interest.

334. An essay entitled, "Genetics and the Hierarchy of Biological Sciences," the presidential address of Sewall Wright at the 10th International Congress of Genetics in Montreal (¶24 ff.), was published in *Science*. This exceedingly thoughtful and thought-provoking exposition has the following main theme as indicated by its subtitle: "Genetics is binding biology at all levels, from macromolecule to species, into a unified discipline." Genetics has done for biology what the atomic theory did for physics and chemistry. In fact, through genetics, all natural science is becoming linked. In few places in the literature can one find such an authoritative and panoramic statement of the past, the present, and perhaps the future of genetics.

335. Wallace and Parsons, working with mice, separately addressed themselves to the problem of affinity. It appears that nonrandom association of markers, which are not linked in the usual sense of being controlled by loci on the same chromosome, may occur due to a tendency at the first meiotic division for centromeres of the same ancestral origin to travel to the same pole. Wallace presents an experimental test for affinity and Parsons describes "quasi linkage" or affinity between linkage groups V and XIII of the house mouse. Affinity, if it occurs in man, would result in recombination (chi) values in excess of 0.5 for traits determined by genes at loci on certain chromosomes, as well as in a simulation of linkage (chi < 0.5) in other circumstances.

336. Hollander and Gowen described an interesting example of "a single-gene antagonism between mother and fetus in the mouse." None such has previously been identified in the mouse. Furthermore, the antagonism they demonstrated differed from the classic incompatibility with erythrocyte antigens demonstrated in man and in livestock in that no erythroblastosis fetalis or hemolytic anemia occurred. In studying a new mutant called "hair loss" (hl) located in linkage group VI and therefore distinct from the "hairless" gene (hr) in group III, they found in mating between hair-loss females (hl hl) and normal heterozygous males a deficiency of normal progeny. The loss did not occur in utero because litter size was normal. The progeny with normal hair were ordinarily born alive but suffered excessive mortality during the first 2 weeks, even when fostered by normal mothers. The clinical syndrome in these mice consisted of inadequate lung inflation, inferior growth, and fragile bones. In the homozygous recessive hair-loss progeny, the hair was lost between the fifth and eighth week, but the animals survived. At birth, therefore, phenotypic classification was not possible. In the progeny of the cross mentioned above, the ratio of offspring with hair loss to those normal was about 2 to 1. In the reciprocal cross of hair-loss male with normal heterozygous female, the ratio was the expected 1 to 1.

337. Hoagland reviewed the role of RNA as an intermediary in protein synthesis. According to the scheme he outlines, DNA is involved in the synthesis of RNA. This "template RNA" resembles the parent DNA in general structure and presumably in its base-pair sequences. However, uracil is substituted for cytosine, and ribose is the sugar component. Template RNA conveys the genetic blueprint from the chromosomes to the ribosomes, which are the site of protein synthesis in the cytoplasm. By a series of synthetic and linking reactions about which information is still sketchy, amino acids are specified and arrayed in protein in accordance with the blueprint derived from the DNA of the chromosomes. Sinsheimer discussed a two-symbol code for DNA.

338. Carlson, who in 1958 proposed that the Rh blood groups represent an example of pseudoallelism (¶158), reviewed in comprehensive manner the work on complex loci in viruses, bacteria, and fungi, as well as higher forms. At the beginning he has an interesting and marvellously prophetic quotation from Muller (Dec. 29, 1921):

". . . If these d'Herelle bodies [phage] were really genes, fundamentally like our chromosome genes, they would give us an utterly new angle from which to attack the gene problems. They are filterable, to some extent isolable, can be handled in test-tubes, and their properties, as shown by their effects on the bacteria, can then be studied after treatment. It would be very rash to call these bodies genes, and yet at present we must confess that there is no distinction known between the gene and them. Hence we cannot categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists and physicists, simultaneously with being zoologists and botanists? Let us hope so."

339. Olsen discussed the interesting parthenogenesis in turkeys with presentation of a "fatherless turkey" who had lived to the age of 42 weeks. He considered two factors essential: (1) a genetically susceptible strain of birds (Proc. Soc. Exper. Biol. & Med. 97:477, 1958) and (2) an activating agent in the blood stream of the hen. The second factor is in some way connected with vaccination for fowlpox (Science 124:1078, 1956). In the eggs from Beltsville Small white females, the frequency of parthenogenic development has now been observed at about 40 per cent! Parthenogenetic birds are always male (J. Hered. 48:217, 1957). They are diploid. (See also J. Exper. Zool. 139:469, 1958.) The female bird is of the heterogametic (ZW) sex. If chromosome doubling occurs in the haploid cell, either ZZ or WW individuals might result; the WW state may be lethal, as the YY state is in Drosophila. Poole showed that the chromosome complements are the same in parthenogenetic and normal turkeys. In both, the average number of macrochromosomes is 18 and the number of microchromosomes varies from 10 to 60.

340. Russell, Russell, and Gower and Welshons and Russell, in important companion papers from the laboratory at Oak Ridge, presented evidence that the Y chromosome determines maleness in the mouse. Prior to 1949 no sex-linked genes were known in the mouse. In that year the character "scurfy," a sex-linked recessive trait, was discovered by Russell. Affected animals showed scaliness first of the tail, then of the rest of the body, tight skin, and late opening of the lids; death of affected males occurred before reproduction. The stock was maintained in the usual manner by breeding of normal males to carrier (heterozygous) females. It was soon observed that occasional affected "females" resulted from this cross. Hypotheses entertained to explain the finding included (1) loss of recessivity ($X^{sf}X$), (2) a high mutation rate in the X chromosome derived from the sire so that the affected female is $X^{sf}X^{sf}$, and (3) sex reversal, i.e., that the affected "female" mouse was really $X^{sf}Y$. The fact that all males from the transplanted scurfy ovaries were affected disproved the first suggestion. The fact that some females from transplanted scurfy ovaries did not transmit scurfy disproved the second. If the third were the case, all females should transmit scurfy and all males should be normal; such was not the case.

Welshons and Russell succeeded in showing, by chromosome studies, that the constitution of scurfy females is XO. Rather than 40 chromosomes, 39 were

present. The XO constitution was also confirmed by crossbreeding experiments with two sex-linked dominant traits.

Russell, Russell, and Gower state that the incidence of XO in mice is at least 0.9 per cent. It is obviously the paternal X chromosome which is lost, at least in the case of scurfy, since the scurfy gene comes from the heterozygous mother. The paternal X chromosome may be lost during spermatogenesis or at the first cleavage of the zygote (with death of the other aneuploid blastomere).

Ohno, Kaplan, and Kinosita, studying meiosis in the mouse, could find no evidence for the formation of XY and O sperm. By exclusion he concluded, therefore, that XO and XXY states in the mouse are better explained by mitotic nondisjunction (see Fig. 6*B*, ¶384) at the first cleavage division.

In the fish *Oryzias latipes*, Yamamoto achieved complete functional sex reversal in genotypic males by administration of estrogens in larval life. Other results of interest in the study were (1) the discovery of fertile YY males, (2) a conclusive demonstration of sex reversal in the genotypic male of the parental generation, and (3) convincing demonstration of partial sex-linkage.

OL.
12
960

341. From Bar Harbor, Green and Dickie published a revised linkage map of the mouse. Eighteen linkage groups are known. The mouse has 20 pairs of chromosomes.

342. Billingham reviewed the subjects of reactions of grafts against the host, the runting syndrome, and related matters. Two implications to man, in particular, were mentioned. Erythroblastosis fetalis may be caused by the entry of maternal leukocytes (rather than free antibody) into the fetus, where they become established as cellular homografts. (Pregnancy in mammals may be regarded as a form of parabiosis or homotransplantation.) Graft versus host reactions must be considered in connection with organ homografts.

Thomas also reviewed the phenomena of homotransplantation immunity, immune tolerance, and the runting syndrome (a form of reaction of a graft against the host). "The runting syndrome [see also Siskind and Thomas] contains, by the way, the implication that any defect in the placenta which might permit maternal reticuloendothelial cells to take up residence in the fetus might lead to serious immunologic difficulties later in life, in a hybrid species." Thomas advanced the theory that survival of the placenta, which is in essence a homograft, is a result of some sort of desensitization by repeated release of trophoblast fragments (fetal tissue) into the maternal circulation.

Parkes demonstrated that pyridoxine deficiency induced either by deficient diet or by pyridoxine antagonists depresses the reaction against homografts in mice. The effect was "greater than that of a single dose of whole-body irradiation in mice and of the same order as that which can be obtained in rats by preconditioning the prospective recipient with suspensions of homologous tissue."

Schultz proposed a genetic hypothesis to account for the apparent paradox of the "laws of transplantation," which demand a community of genetic constitution between donor and recipient, and the experiments in which tolerance is induced, or histocompatibility barriers are overriden, or tumors are enhanced

in their growth or adapted to their hosts. He suggested serotypes in Paramecium as a possible model system. A chromosomal mechanism was proposed.

Fox discussed the genetics of sex-specific antigens. Eichwald, Lustgraf, and Strainer reported studies of genetic factors in parabiosis.

343. Lederberg expounded a genetic theory of antibody specificity which should prove useful as a guide to the design of experiments to test the hypothesis. Essentially, the theory suggests that antigens, rather than bearing instructions for antibody specificity, select cell lines that arise by mutation. "Elective theories" of the type proposed (and distinct from "instructive theories") date from Ehrlich and have been explicitly stated by Talmage and by Burnet in terms of cellular selection. Crediting Burnet (see ¶295) with the theoretic formulation, Lederberg expanded the hypothesis and stated it in nine propositions, of which the fifth (*e*) is central to the elective theory:

a. The stereospecific segment of each antibody globulin is determined by a unique sequence of amino acids.

b. The cell making a given antibody has a correspondingly unique sequence of nucleotides in a segment of its chromosomal DNA (its "gene for globulin synthesis").

c. The genic diversity of the precursors of antibody-forming cells arises from a high rate of spontaneous mutation during their lifelong proliferation.

d. This hypermutability consists of the random assembly of the DNA of the "globulin gene" during certain stages of cellular proliferation.

e. Each cell, as it begins to mature, spontaneously produces small amounts of the antibody corresponding to its own genotype. Each cell specifies only one type of antibody. There appears to be support for this view in the work of Nossel.

f. The immature antibody-forming cell is hypersensitive to an antigen-antibody combination; it is suppressed if it encounters the homologous antigen at this time. The distinction between the function of an antigen as inhibitor (self-marker) or as inducer of antibody formation is considered to be the stage at which the antigen is introduced into the potential antibody-producing cell. Maturation may be defined in terms of the progression of the cell from sensitivity to reactivity.

g. The mature antibody-forming cell is reactive to an antigen-antibody combination. It will be stimulated if it first encounters the homologous antigen at this time. The stimulation comprises the acceleration of protein synthesis and the cytologic maturation which mark a "plasma cell."

h. Mature cells proliferate extensively under antigenic stimulation but are genetically stable and therefore generate large clones genotypically preadapted to produce the homologous antibody.

i. These clones tend to persist after the disappearance of the antigen, retaining their capacity to react promptly to its later reintroduction.

344. Serra suggested that "gene conversion" is due to intragenic crossing over with position effects. What was interpreted as gene conversion was described in cysteine mutants of Neurospora by Stadler.

VOL. 12 196

345. The mutagenic effects of caffeine demonstrated earlier in bacteria and fungi were confirmed in Drosophila by Andrews. Previously, Novick and Szilard found that guanosine, adenosine, and niosine prevented mutation from theophylline and caffeine and also reduced the spontaneous mutation rate by one-half or one-third. Adenine was especially effective (Novick, 1956). In this "age of polypharmacy," the mutagenic effects of drugs are potentially of great significance; information on this point is lamentably scant. With reference to caffeine, Andrews pointed out, "Repeated small doses of this drug may, in the long term, compensate for its intrinsically weak mutagenic activity."

346. The September, 1959, issue of *Scientific American* contained a well-illustrated and well-written symposium on ionizing radiation. The contributors and topics were as follows:

a. Platzman, R. L., Argonne National Laboratory: What Is Ionizing Radiation?

b. Arnold, J. R., University of California at La Jolla, and Martell, E. A., U. S. Air Force: The Circulation of Isotopes.

c. Hollaender, A., and Stapleton, G. E., Oak Ridge: Radiation and the Cell.

d. Loutit, J. F., Harwell: Ionizing Radiation and the Whole Animal.

e. Crow, J. F., University of Wisconsin: Ionizing Radiation and Evolution.

f. Warren, Shields, Harvard University: Ionizing Radiation and Medicine.

g. Charlesby, A., Royal Military College of Science, England: Ionizing Radiation and Organic Chemistry.

h. Billington, D. S., Oak Ridge: Ionizing Radiation and Metals.

i. Beadle, G. W., California Institute of Technology: Ionizing Radiation and the Citizen.

Scott and Evans edited the proceedings of a conference held on May 2, 1958. It was attended by four professors of genetics, four professors of radiobiology, and twenty-one professors of radiology and was designed for geneticists and radiobiologists to teach radiologists about genetic hazards and for radiologists to demonstrate what is being done to minimize radiation exposure of the gonads. Titus Evans and George H. Mickey discussed the mechanism of radiation damage. Irwin Herskowitz covered the factors affecting radiation-induced mutation rates. James F. Crow reviewed population aspects. W. L. Russell enumerated eighteen points concerning mammalian radiation genetics:

a. Spermatogonia—at least some of them—are very sensitive to irradiation. However, mice recover from as much as 1,000 r of acute x-ray exposure to the testis with no higher rate of infertility than in unexposed groups.

b. Chromosomal aberrations are induced in males in the later stages of spermatogenesis—spermatocytes possibly, spermatids definitely, and sperm definitely.

c. Oogonia are not present in the adult mammal. The female germ cells are present as primary oocytes. They are liable to radiation-induced aberrations. Dominant lethals, produced by irradiation of the female, die at a very early stage.

d. Translocations express themselves in descendant generations by semisterility. But a very low rate of translocations from irradiated females was found.

e. At high dosage level there is a departure from a linear relationship between dosage and the rate of point mutations. For example, there is a drop below the expected rate at dosages of 500 to 1,000 r.

f. A corollary to point *e*: It is possible that the mutation rate at lower dosage levels is greater than previously thought.

g. The mutation rate is lower for chronic exposure than for acute exposure at the same level of total dosage (¶61).

h. The three preceding points indicate the complexity of the relationships of mutation rate to dose and dose rate. For extrapolating to man it seems prudent to use the highest mutation rate found in the mouse: 28×10^{-8} per r per locus (in 300 r of acute irradiation).

i. Mutation effects of acute irradiation are difficult to study in the female because sterility is produced by relatively small doses. Chronic γ irradiation of the female results in only a low mutation rate.

j. There is in mammals no clear evidence of recovery from genetic damage.

k. A factor of over 30 separates the highest rate and the lowest mutation rates at the seven loci used by Russell in his studies in mice.

l. Most changes induced in spermatogonia seem to be point mutations. On the other hand those in irradiated sperm are often deletions.

m. In the seven loci studied there are significant differences in the proportion of mutations that turn out to be recessive lethals.

n. In mice the recessive lethals kill late, e.g., at the weanling age, and would, assuming comparable circumstances in man, be "tragedies in human experience."

o. Some of the recessive lethals have obvious effects, such as stunting of growth, in the heterozygous state.

p. Effects in heterozygotes can be demonstrated statistically with others of the recessive lethals.

q. Survival to 3 weeks is reduced in heterozygous carriers of a recessive lethal.

r. After deaths in the first 3 weeks are excluded, the lifespan of surviving mice, offspring from irradiated fathers, is shortened (e.g., 0.6 days per rep of neutron irradiation to the father).

347. Szilard proposed a theory of aging based on somatic mutation. According to his theory an increasing number of cells are rendered inviable by successive "hits"—either when two homologous chromosomes have suffered a hit or when one of a pair of homologues has suffered a hit and the other carries an inherited recessive "fault." Death comes when a certain proportion of cells are thus rendered ineffective. In answer, John Maynard Smith pointed to work in Drosophila: (1) Inbred strains which survived to adult life would be expected to be heterozygous for fewer faults than outbred wild populations; they should then live longer. Such is not the fact. (2) Drosophila f_1 hydrids between two inbred lines would be expected to be intermediate in load of faults as compared with the

VOL. 12 1960

two parental lines; hybrid longevity should therefore be intermediate. Such is not the observation. (3) Maintenance of flies at higher temperatures should accelerate aging; within limits it may actually increase longevity. (4) Male flies with a single X chromosome should be more vulnerable than females; however, males have as great longevity as do females.

Sandler and colleagues described work on "meiotic drive," the term used by the authors to describe segregation distortion, or preferential segregation, where heterozygotes do not produce two kinds of gametes in the expected 1 to 1 ratio. Previously reported examples in Drosophila, maize, tobacco, and mice were reviewed (see ¶328). The authors specifically reported experimental data which indicate that a genetic element located near the proximal heterochromatin of the right arm of chromosome II and called "segregation distorter" (SD) has certain properties, among them: (1) when paired with a structurally normal chromosome in a male, it is recovered five to ten times more often than the homologous normal chromosome; (2) no effect is observed in the female; and (3) some structurally abnormal chromosomes suppress the effect, which suggests that normal synapsis is necessary for SD to operate. The abnormal segregation ratio can be shown to result from the effect of the normal allele at the SD locus rendering the gamete inactive. The postulated cytogenetic basis for the phenomenon assumes (1) that SD causes a break in the normal-SD homologous chromosome which undergoes a sister union forming a bridge at anaphase II and (2) that the bridge (or its breakage product) is lethal for the resultant cells. Preliminary cytologic confirmation for the hypothesis was presented.

348. Wright considered the mathematical framework of the theory of evolution at a succession of levels of complexity: the separate genes, the genome, and the population. Burnett reviewed virus genetics.

IV. HUMAN AND MEDICAL GENETICS, GENERAL CONSIDERATIONS

349. Reviews. In a long review, "Modern Problems in Human Genetics," Vogel discussed the following topics:

The chromosome count in man
Proof of genetic hypotheses
New aspects of the twin method
Rare modes of inheritance in man such as X-linked dominance and the questionable Y-linked and incompletely sex-linked inheritance
Autosomal linkage in man
The interaction of genes
Methods for estimating mutation rate in man
Germinal mosaicism and delayed mutation
Inborn errors of metabolism
Detection of heterozygotes
Blood groups and disease
Pharmacogenetics
Balanced polymorphism

Lerman provided a review article entitled, "Chemistry, Heredity and Disease."

Childs gave an orienting discussion of medical genetics, pointing out among other useful aspects the relative nature of dominance, recessivity, and penetrance. "The genetic constitution possessed by the individual provides him with a long list of potentialities which are or are not realized depending upon the kinds of environment in which it is called upon to function."

In a group of papers published together in *Practitioner*, Sorsby discussed "Principles of Heredity"; Carter, "Heredity and Congenital Malformations"; Cowie, "Heredity and Mental Disease"; Parkin, "Blood Groups and Heredity"; Motulsky and Gartler, "Consanguinity and Marriage"; Crew, "Heredity and Sex-determination"; and Bender, "Twins and Heredity."

350. Linkage. Renwick listed the uses, realized or potential, which study of *genetic linkage in man* can serve:

Basic cartography of the human germ plasm should be possible.
Heterogeneity in diseases which are phenotypically identical can be demonstrated.
Heterogeneity can be excluded—valuable information in estimating mutation rates in man.
The allelism of specific genes can be tested.
Allelism can be excluded.
The passage of an "abnormal gene" can be traced through a family for early detection of the genetically affected person.
Because of the haploid character of the sperm, linkage relationships may be used to separate sperms carrying a "bad gene."

Grobin confused terminology by writing that "certain diseases are almost sex-linked"; he referred to the preponderant occurrence of angina pectoris, myocardial infarction, peptic ulcer, etc., in men and of gallbladder disease, goiter, hypochromic anemia, etc., in women. The loose usage of the term "linkage" in the medical literature is to be discouraged. It should be used only in the true genetic sense, to indicate that the loci determining two polymorphic traits are situated on the same chromosome pair. Linkage is *not* (1) *association* between particular blood group phenotypes and specific diseases, e.g., O and peptic ulcer, or (2) *syndromal relationship*, as in the several manifestations of the Marfan syndrome which are the result of a single mutant gene. "Sex-linkage" is a term which, as is illustrated by Grobin's comment, is also abused in the general medical literature. It should not be used for sex-influenced or sex-limited traits not controlled by loci on the sex chromosomes.

Polymorphic systems in man (Allison): "Polymorphism may be defined as the occurrence together in the same habitat of two or more discontinuous forms of a species in such proportions that the rarest of them cannot be maintained merely by recurrent mutation." (Ford, 1956.)

VOL. 12 1960

351. The blood level of free isoniazid, isonicotinic acid hydrazide (INH), after a single standard oral dose seems to be determined as a simple Mendelian trait (¶323), which may prove useful as a genetic marker. Leifheit and Smith described a relatively simple chemical method for determination of free INH in blood. Jenne studied INH metabolism by the use of rapid intravenous injection of 5 mg. of INH per kilogram of body weight and the chemical determination of free INH at 0, 30, 90, and 150 minutes. The half-life was determined from the fall-off curve. Knight, Selin, and Harris used a microbiologic method of assay. The frequency of rapid inactivators was greater in Japanese than in Europeans. In twenty families the observations were consistent with the hypothesis that rapid inactivation is dominant to slow.

352. Haptoglobins. Smithies described a modified technique for starch gel electrophoresis (used in the study of haptoglobins and transferrins) which consists of a vertical positioning of the trays and permits direct application of liquid samples. The resolving power and reproducibility of the method were thereby thought to be improved. In the same report, evidence was presented that genetic factors are involved in variations in the serum proteins which migrate immediately behind albumin.

L.
2
60

Haptoglobin methods were also discussed by Nyman and by Laurett, among others. Steinbach and Pejaudier described separation of haptoglobins from plasma fraction IV by subfractionation.

Connell and Smithies purified and quantified the haptoglobins of the three common types and one modified type, Hp 2-1 (mod.). Evidence was presented that the haptoglobins were not damaged in purification and that multiple haptoglobin zones demonstrated by starch gel electrophoresis are not artefacts but represent distinct protein components. Mäkelä, Eriksson, and Lehtovaara, in Finland, found gene frequencies of $Hp^1 = 0.362$ and $Hp^2 = 0.638$. No close linkage was demonstrated in family data. Like several other groups, they encountered and scrutinized the "undeveloped" pattern, called ahaptoglobinemia by others. That there is not a "silent" allele at the Hp locus responsible for the ahaptoglobinemic state is argued by the fact that 2-1 mothers have had ahaptoglobinemic children. More likely is the view that these patients are homozygous for a recessive suppressor gene at another locus.

Bearn and Franklin have demonstrated the fact, of theoretic interest to the problem of gene action in protein synthesis, that the haptoglobin synthesized by the heterozygote is not a mixture of the haptoglobin produced by the two homozygotes but rather a hybrid protein with distinctive physical properties. The state of aggregation of two proteins may be responsible for the observed properties, as suggested by Smithies.

Javid and colleagues concluded that myoglobin is not bound by haptoglobins or other plasma proteins. The "low renal threshold" for myoglobin is due to the lack of binding.

353. Transferrins. Smithies and Hiller provided an important work on the genetic control of transferrins (β globulins). Family data strongly suggest that

the transferrins are controlled at a single autosomal locus at which at least three alleles can substitute. The symbol "Tf" was suggested for the locus; the alleles can be designated Tf^B, Tf^C, and Tf^D. Tf^C is the common allele in all populations so far sampled. Tf^B occurs in approximately one of 100 Canadian white persons. Tf^D occurs in about one of 25 New York Negroes and one of 10 Australian aborigines but has not been found in over 500 white persons tested. Four of the six possible genotypes have been observed, Tf^{BC}, Tf^{CC}, Tf^{CD}, and Tf^{DD}. There is independent segregation (i.e., no linkage) of the Tf locus and those for ABO, MNS, P, Rh, and haptoglobins.

Giblett, Hickman, and Smithies amplified the description of the transferrins. First, they confirmed that the various β globulins are iron binders by means of radioautographs of starch gel electrophoresed specimens treated with Fe^{59}. Second, they pointed out that at the time of their writing eight transferrins were known.

Most specimens show only C. Three β globulins migrating faster than C have been found only in white persons. These have been termed:

B_0 (B_0C was present in about one of each 100 American white persons)
B_1
B_2 (B_2C was present in 5 of 425 white Canadians [Smithies, 1958] and one of 139 white Britons [Harris])

Four β globulins migrating less rapidly than C have been found only in colored peoples—Australian aborigines and American Negroes. These are the following:

D_0 (CD_0 was found in one of 493 American Negroes)
D_1 (CD_1 was found in about 10 per cent of Australian aborigines and American Negroes)
D_2
D_3 (CD_3 was found in one of 493 American Negroes in Seattle)

(Ashton described the β-globulin types in Zebu cattle. Six β-globulin alleles have now been identified in cattle and fourteen of the fifteen possible phenotypes have been identified. Ashton also presented evidence for a selective elimination of bovine fetuses unlike the dam with respect to β-globulin type.)

354. Gm system. In the Gm system of serologically different γ globulins detected by a capacity to inhibit agglutination of red cells (coated with incomplete anti-D serum) by the serum of rheumatoid arthritics (¶'s 71, 324, 320*n*), several members have been identified:

Gm^a—Grubb and Laurell
Gm^b—Harboe
Gm^x—Harboe
(Gm^y, the postulated counterpart of Gm^x, has not yet been found)
Gm-like (Steinberg) (¶324)

The interrelationship of these factors has not been completely elucidated. It seems that Gm^a and Gm^b are complementary.

Harboe, in another publication, pointed out that the hemagglutination-inhibition reaction used in determining Gm type is quantitative, like the PTC taste tests and the tests of ABH secretion. Furthermore he reported quantitative studies of the system.

In Finland, Julkunen and Tiilikainen found a significant increase in the frequency of Gm (a+) in patients with rheumatoid arthritis and suggested that hyperglobulinemia may be responsible. Gm (a+) appeared in 80.4 per cent of the cases of rheumatoid arthritis with a γ globulin percentage over 25—as compared with a frequency of 65 per cent in the Finnish population generally. The authors commented, as had Grubb (¶320*n*), that family studies with reference to rheumatoid arthritis might be revealing.

(Polymorphism has similarly been demonstrated in the γ globulins of the rabbit by precipitation reactions [Dubiski and associates; Dray and Young].)

OL.
12
960

355. Earle and colleagues reported on a large family with a double albumin peak by electrophoresis (see ¶74). Wuhrmann found a double albumin peak in four members of three generations of a family in the canton of Zürich. In the proband, a diabetic, the anomaly was apparently not a constant feature but was present only during diabetic coma or "precoma."

356. Fraser, Harris, and Robson detected an unusual plasma protein by starch gel electrophoresis in several members of one family. The probable mechanism of inheritance was autosomal dominant. No close linkage was evident.

357. Two reports on a study of the biochemical genetics of β-amino-isobutyric (BAIB) aciduria by Gartler appeared. BAIB is an amino acid of non-protein origin. Polymorphism with respect to its excretion was thought by Crumpler and co-workers (1951) to be based on a genetic difference in tubular function. The lack of elevated plasma levels in high excreters was thought to exclude a defect in the intermediary metabolism of BAIB. From the experience with alkaptonuria it is clear, however, that for substances poorly reabsorbed from the glomerular filtrate, plasma level is not critical. Furthermore, Gartler could find no evidence of difference in renal handling of BAIB in high and low excreters. The possibility of a block in precursor metabolism (thymine $\rightleftharpoons$ dihydrothymine $\rightleftharpoons$ β-ureidoisobutyric acid $\rightarrow$ BAIB) was excluded by Gartler. The experiments suggested that the difference between high and low excreters is a matter of differential metabolism. Low excreters retained most of an administered load, whereas high excreters eliminated 50 per cent or more. Details of the metabolic difference are unknown.

Blumberg and Gartler found the highest frequency of high excreters of BAIB in the Marshallese Micronesians—86 and 83 per cent, as compared with 10 per cent in white persons in the United States, 23 per cent in Alaskan Eskimos, 56 per cent in Alaskan Athabascan Indians (Allison, Blumberg, and Gartler), and 59 per cent in Apache Indians.

Rubini and coauthors found that BAIB excretion is a sensitive index of radiation exposure.

358. The yeast *Hansenela wingei* is of two mating types which agglutinate when mixed (Wickerham, 1956). It had been observed that human serum inhibits the agglutination. Steinberg and Giles found that only some human sera possessed the capacity of inhibition. In both Negro and white persons (in Cleveland) about 46 per cent inhibited agglutination. In a study of fifty-five families, the distribution of mating types agreed with the expected values on the assumption that inhibition is dominant. Furthermore, the data from offspring are consistent with this hypothesis. Specifically, none of 40 children from 2 noninhibitor parents were inhibitors. The capacity to inhibit is less frequent in children, which suggests that an antibody-antigen reaction is involved and that exposure to yeast antigen is a necessary environmental factor, but that the genetic constitution of the individual is likewise an essential feature.

359. Bell and Williams demonstrated, using twin calves, that a genetic factor operates in threshold taste discrimination. Nachman studied the inheritance of saccharin preference in Sprague-Dawley albino rats.

Tuberculous patients do not differ from controls in the proportions of PTC tasters and nontasters (Åkesson) (see ¶'s 532, 535.).

Dencker, Hauge, and Kaij again underscored the fact that the *PTC test* is not of the same quality as the serologic characters as a criterion of zygosity or parentage or for linkage work. In 28 pairs of adult monochorionic twins, they found concordance in 26. In the other 2 pairs, both female, obvious discordance was observed at first test. On extensive testing 5 months later, both pairs were found to be concordant. On another retesting 9 months after the first test, one of the pairs again showed marked discordance. The cause of the variations was not evident. The observations appear to demonstrate that exogenous modifiers may vary in their effect within a relatively brief period.

Fischer and Griffin wrote on the mechanism of PTC tasting; they maintained that a salivary factor is essential and speculated that the genetic variation in PTC tasting may be related to genetic variation in a salivary enzyme, specifically tyrosine iodinase. The authors make the interesting statement that "the taste threshold for PTC is apparently distributed as a continuum at birth and becomes only gradually bimodal during the growth process."

360. Matsunaga presented evidence for a "dosage effect," i.e., incomplete dominance, of the gene for secretion of blood group antigens in human saliva. The mean titer of Se se children (born from Se-- × se se matings) was 7.1765, while that of Se-- children born from Se-- × Se-- matings was 7.7167 and that of Se-- children born from Se-- × Se-- matings with no se se children was 7.8012. These differences were not significant. However, a highly significant difference in titer was observed between the Se-- parents of Se-- × Se-- matings with no se se children (7.7101) and Se se parents (6.1379) ascertained by the occurrence of at least one se se child (see also ¶'s 491, 509).

(For a discussion of the blood group and secretor polymorphic conditions see ¶491 ff. For a discussion of the hemoglobin polymorphic states see ¶472 ff.

In light of the individual variations in blood pH found in man by Shock and Hastings (1934), Wolfe's description of blood-pH differences in two inbred strains of mice is of interest.

Greulich insisted there are highly individualistic variations in x-ray films of the hand and wrist which could be useful in the personal identification. Seventy pairs of twins of like sex were studied.

Biochemical polymorphic conditions identified in farm animals now include (Ogden) hemoglobins (in ruminants), β lactoglobulins, and probably a lactalbumin of cow's milk, sodium-potassium concentrations of erythrocytes, catalase of dog erythrocytes, esterase activity in swine, and β globulins of cattle (¶353).

Twins: 361. Nance provided a useful review of twinning. The following areas were covered: (1) historical background, (2) Weinberg's differential method (number of monozygotic twins equals total number of twins minus twice the number of twins of unlike sex), (3) the stages of twinning, (4) Siamese twins, (5) mirror imaging ("Shakespeare, . . . himself the father of fraternal twins . . . had Droniro say to his brother in the *Comedy of Errors*, 'Methinks you are my glas [*sic*] and not my brother.' "), (6) diagnosis of zygosity by examination of the membranes, (7) diagnosis of zygosity by the similarity method of Siemens, (8) the possibility of other types of twinning (e.g., fertilization by two different sperms of a divided egg or fertilization of the second polar body), (9) the incidence and heredity of the multiple-birth process, (10) application of the twin method in nature-nurture investigations, (11) biases from circulatory anastomoses, and (12) chimerism.

Bulmer claims to be able to demonstrate a fall in the twinning rate in countries occupied by Germany in World War II. Decrease in litter size in malnourished animals was the point of departure for the study.

Millis, working in Singapore, confirmed the low incidence of dizygotic twinning in the Chinese and Japanese as compared with Caucasian and Negroid people. The frequency of both monozygotic and dizygotic twinning increased with maternal age in the Chinese, but at all ages monozygotic twinning was more frequent. In Caucasians the frequency of monozygotic twinning is independent of maternal age (zygosity was estimated by Weinberg's method). (Fig. 1).

Detailed tables of twin births in Italy have been published since 1949. Bulmer analyzed the effect of parental age (Fig. 1), parity, and duration of marriage on the twinning rate. The rate of dizygotic, but not monozygotic, twinning increases with parity independent of maternal age. The twinning rate is higher in pregnancies conceived during the first 3 months of marriage than it is in those conceived later in marriage or before marriage.

In 4 sets of monozygotic twins, Kerr observed polycythemia in one and anemia in the other. One twin looked plethoric, the other twin pale with palpable spleen tip and reticulocytosis of the peripheral blood. Half of the single placenta was grossly congested with tortuous vessels, whereas the other half was pale with collapsed vessels. The author suggested a communication between the circulations of the two fetuses and a trap mechanism by which blood is prevented

from leaving one fetus and its placental portion and prevented from entering the other fetus. The nature of the obstruction is unknown. This condition in mild form may be very common. Here is a mechanism for dissimilarity of "identical" twins. Reference is made to the reports of markedly dissimilar monozygotic twins.

Matsunaga examined the question of whether there may be, in addition to monozygotic and dizygotic twins, a third type which arises from fertilization of an ovum and of a giant polar body by different sperms. There is so far no cytologic evidence for such a type of twinning in higher animals. Evidence of its occurrence might be provided by studies of the frequency of concordance of twins with regard to allele pairs for which the mother is heterozygous. In 1952 Matsunaga studied twins of unlike sex from matings of MN mothers with fathers who were either blood group M or blood group N. An observed excess of concordant pairs was significant at the 5 per cent level when compared with the expected 1 to 1 ratio. A further series of 92 pairs of twins of unlike sex was studied with similar results. However, the author had evidence that the MN blood

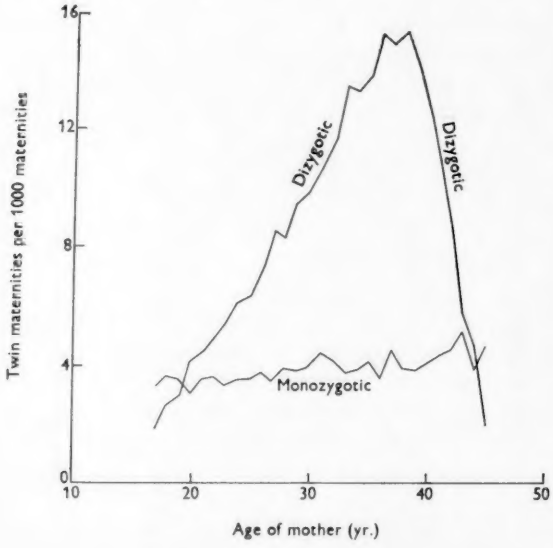


Fig. 1.—Maternal age and twinning. Data from Italy, 1949 to 1954. (From Bulmer, M.G.: Ann. Human Genet. 23:454, 1959.)

groups are not neutral from the point of view of natural selection. When, as control, he used not the 1 to 1 ratio but the ratio of concordant and discordant pairs from MN fathers and M or N mothers, no difference was demonstrable. Therefore, the question of a third type of twinning remains unanswered.

Aird presented his uniquely extensive experience with *conjoined twins.* The most interesting part of the discussion is that concerning the zygosity of conjoined twins. Although it seemed most likely to the author that such twins are monozygotic, the possibility of fusion of two separate blastomeres was left

open. A most remarkable case is referred to in which one conjoined twin was apparently a normal male and the other was eunuchoid with "no detectable testes." Freemartin status was postulated. A chromosomal aberration resulting in the Klinefelter syndrome in the eunuchoidal individual seems possible. Corner (1955) concluded that conjoined twins are formed through duplication relatively late (about 15 days) after fertilization (Annotation). There is an intriguing impression that conjoined twins occur especially often among natives of Nigeria. Allen, Metcalf, and Giering discussed anesthetic management for separation of conjoined twins and pointed out that acute adrenal crisis may occur in one twin soon after separation, presumably because of dependence on the adrenal of the mate.

362. Ueno, Suzuki, and Yamagawa demonstrated erythrocyte *chimerism* in a 12½-year-old girl, one of twins of unlike sex. The twin brother did not show chimerism. (In two previous reports of chimeric individuals, both twins showed the mixture.) By primary agglutination with anti-A serum, the chimeric child was found to have type O and type A blood in a ratio of 31.6 to 68.4 on one count and 30.4 to 69.6 on another made after a lapse of one year. There was no sex abnormality. The chimerism extended also to the MN system, a circumstance which made somatic mutation unlikely. The authors thought that O blood was inherited and A blood "grafted from her twin brother by intrafetal anastomosis." A antigen as well as H was secreted in the saliva. The children of the girl will be of great interest.

Woodruff and Lennox found that reciprocal skin grafts were retained in a pair of twins showing blood chimerism. The blood groups in the pair of 21-year-old twins of unlike sex were as follows:

	A	O
Male twin	86 per cent	14 per cent
Female twin	1 per cent	99 per cent

In the female, the graft retained the coarse male skin pattern, and vice versa. In both, nuclear sexing suggested that some of the donor cells survived and that the grafts were partially replaced by fibroblasts from the recipient.

363. Radiation. In a discussion of radiation hazards, Schull emphasized the difficulties in precise appraisal of either somatic or genetic effects.

Kaplan followed up 566 children and grandchildren of 644 women whom he had treated for infertility with about 65 r to the ovaries. The follow-up was as long as 33 years after the treatment in some cases. He concluded that no definite effects could be demonstrated. Friedell, in the discussion, pointed out that induced recessive mutations would escape attention and that sex-linked recessive traits with preferential mortality in males should be sought. It may be significant that all 11 postnatal deaths in this series occurred in males. The amazing part of Kaplan's report was the revelation that such treatment has been used to the very present, despite the long familiar mutagenic effects on germinal tissue. In a personal communication Kaplan reports that he and other

radiologists continue to use x-ray therapy for infertility because they have been convinced of its effectiveness and safety.

(For a discussion of radiation and leukemia see ¶463.)

364. Population genetics. Kallmann and Rainer gave a general review.

365. Heredity counseling. Thompson described a new heredity counseling service at the University of Alberta in Edmonton. It is described as the first of its kind in Western Canada. The scientific value and professional usefulness of the venture is reduced by his following statement: "We find it necessary for reasons of medical ethics, to accept the diagnosis provided by the referring physician, even when its accuracy is doubtful." Genetic counseling *must* rest on a firm foundation of accurate diagnosis. (The author makes the following reprehensible statement: "Fortunately it is not always necessary to have an accurate diagnosis in order to identify a hereditary pattern.") The role of a medical genetics clinic must not be merely to render a cursory impression of pattern of inheritance but also to assist in the diagnosis. The staff of a medical genetics unit is likely to have had more experience with rare, Mendelizing disease traits than most practitioners. There are really no "reasons of medical ethics" to prevent a genetics counseling unit from insisting that the referring physician submit whatever diagnostic information is available. Neither is there any reason why necessary diagnostic tests cannot be done under the direction of the medical genetics unit. These are the well-established and well-accepted procedures when any patient is referred to a specialist for consultation and opinion. The patient, the referring physician, and the counseling service will learn little unless the cases in question are investigated in detail in accordance with the highest standards of clinical practice.

Myrianthopoulos, geneticist, and Stevens, physician-neurologist, announced a genetic counseling service for the Washington, D. C., area.

Miscellaneous: 366. Falek studied handedness in a group of New York City school children and their immediate families. An increase in the proportion of left-handed children was found only from matings of right-handed fathers and left-handed mothers. Other aspects of the study suggested collaboration of a genetic factor and early home training in determination of handedness. The factor of parental pressure is minimal in two mating groups: (1) right-handed father with left-handed mother and (2) two right-handed parents. (Left-handed fathers may be particularly cognizant of the economic and social handicaps of left-handedness and more likely to attempt to change the handedness of the child.)

367. Sutton presented data on 403 subjects, purporting to indicate an association between eye color (i.e., iris color) and reaction to pain with dental drilling. The subjects were Australians of European descent. The darker the eyes, the greater was the reaction of pain.

VOL. 12 196

368. Of tangential interest to human genetics are birth control measures applicable on a large scale. Pincus and eight collaborators reported on a study in Puerto Rico and Haiti in which one tablet a day of an estrogen-progesterone combination was given orally to women from the fifth to the twenty-fourth day of their menstrual cycle as contraceptive. They concluded that this is an effective contraceptive measure, with no abnormality produced in the menstrual cycle, no adverse effects on general physiologic condition or sex life, and no impairment of fertility after the agent is discontinued.

369. Osborne and DeGeorge demonstrated, by twin analysis, a genetic component in the *erythrocyte sedimentation rate.* Monozygotic twins had more similar values than did dizygotic twins.

370. Friberg and colleagues did a study of *smoking habits* in 59 monozygotic and 59 dizygotic twin pairs. Presumably the dizygotic twins were of like sex, but this was not explicitly stated by the authors. Zygosity was determined using haptoglobin type, blood groups, and anthropologic methods. Most of the information was obtained by personal interview. The results showed greater concordance in monozygotic twins than in dizygotic twins. Fisher (¶287) had reported greater concordance in monozygotic twins brought up apart; in fact, the concordance rate in this group was as high as in the group of monozygotic twins brought up together. Although these data strongly indicate that one's constitution in its broadest meaning, including temperament and personality, determines likelihood to smoke, there is, of course, no evidence in these data of a constitutional tendency to lung cancer.

Horn and colleagues studied smoking in teen-agers. Table III presents the findings according to parental smoking.

TABLE III

	PROPORTION OF CHILDREN REGULAR SMOKERS	
	BOYS	GIRLS
Neither parent smoked	16.7	6.8
Only father smoked	26.3	12.4
Only mother smoked	23.6	18.1
Both parents smoked	31.9	18.5

These findings are not unexpected for a socially conditioned trait. Yet the result is also what would be expected of a trait which is appreciably genetic in its determination (see ¶373).

Selzer studied the relationship between a body-build rating made from 1938 to 1942 on Harvard College sophomores and their smoking history during the next 15 years. The aspect of body build involved was that termed "masculine component." The author claimed that with the aid of standard charts it was possible to characterize individuals readily as having a strong, moderate, weak, or very weak masculine component. Weakness of the masculine component was more frequent in smokers than in nonsmokers. However, the differences were significant only at something less than the 0.05 level, and the numbers in most

classes were distressingly small. The author appears to favor a genetic hypothesis for the correlation. A social basis seems possible. Experience with collegiate life would seem to suggest that the cigarette habit is more likely to become established in the nonathletic type with a lesser "masculine component," that is, in the type which by Selzer's own statement shows more interest in the arts, philosophy, social science, and the like.

371. The future. Hermann J. Muller has a reputation for an uncanny insight into the future of genetics (see ¶338 for an example). Furthermore, as Peters writes (¶310 [*j*]), "Once in a great while, however, science is blessed with an author both eminently successful in his trade and articulate, so that his contributions are a pleasure to read. Such a man is H. J. Muller." In a provocative article entitled, "The Guidance of Human Evolution," Muller addressed himself in a new way to the old theme that man should guide his own evolution—positive eugenics. Specifically, for example, artificial insemination is, in his opinion, not only not practiced as widely as it should be, but fullest advantage is not taken of the opportunity to observe the results of the practice. Muller dissuades the reader from any view that the present stage of evolution attained by man is optimum even for existing environmental circumstances. He cites examples that would represent an improvement: reducing the need for sleep, bringing the induction of sedation and stimulation under better voluntary control, and upgrading general intelligence coordinated with an even greater improvement in "the genetic basis of our moral natures." Speech, a method of communication which is "pitifully slow and plodding compared with the river flow of ideas," could profitably be substituted for by better ones for which biologic precedence exists. The political mechanics necessary for man's control of his evolutionary destiny have, unfortunately, not been worked out.

VOL. 12 196

V. METHODS

Statistical methods: 372. It is perfectly clear (1) that the parents of individuals affected by a rare recessive trait (with the genotype aa) are usually normal (with the genotype Aa); (2) that sibships ascertained by the occurrence of at least one affected member will not include those sibships which are offspring from 2 appropriately Aa parents but which by chance do not include an affected member; (3) that, because of the last fact, ascertainable families will contain, on an average, more than one affected child in every 4 as predicted by Mendelianism; and (4) that the appropriate correction for the bias depends on the particular method of ascertainment. At least three authors addressed themselves to this problem previously studied by Weinberg, Haldane, Fisher, Bailey, and others: Newton E. Morton, "Genetic Tests Under Incomplete Ascertainment"; A. G. Steinberg, "Methodology in Human Genetics"; and C. A. B. Smith, "A Note on the Effects of Method of Ascertainment on Segregation Ratios."

Three types of ascertainment are practiced; a different correction is appropriate to each. Practically speaking, it may be difficult to know the precise statistical properties of the method used in collecting the particular body of data.

The three types of ascertainment are as follows:

a. Truncate selection (Morton), or complete ascertainment (Smith), where all sibships with at least one affected person are included (or a random sample of all such sibships) and the probability of including a family does not depend on the number of normal or affected siblings, provided at least one is affected.

b. Single selection (Morton), or Smith's case 2, where the chance of ascertainment is so small that there will be only one proband per family.

c. Multiple selection (Morton), or Smith's case 3, where the chance of ascertainment is constant for each individual.

Kaelin examined the same problems with reference to sex-linked recessive traits and with reference to data on the syndrome of testicular feminization (¶552) published by Taillard and Prader (J. génét. humaine 6:13, 1957).

373. Lilienfeld demonstrated that a binomial model, used to determine the consistency of observations with a recessive gene hypothesis, has a low ability to discriminate between genetic and nongenetic hypotheses. The binomial test, as referred to by the author, is based on the Hardy-Weinberg principle and on

TABLE IV. COMPARISON OF OBSERVED AND EXPECTED NUMBERS OF PARENTAL MATING CLASSES AMONG OFFSPRING ATTENDING MEDICAL SCHOOL

	NUMBER OF MEDICAL STUDENTS IN MATING CLASS	
PARENTAL MATING CLASS	OBSERVED	EXPECTED
Both parents physicians	0	1.0
One parent a physician	32	30.0
Neither parent a physician	229	230.0
Total	261	261.0
p (gene frequency)	0.0613	
Chi square (1 d.f.)	1.14	
P	$0.30 > P > 0.20$	

the fact that the frequencies of the three parental mating types are binomially distributed. The proportions of parents both affected, one affected, and neither affected are represented, respectively, by p^2, $2pq$, and q^2, where p is the frequency of a presumed "recessive" gene under test and q is $1-p$. The gene frequency (p) is determined from the frequency of the presumed recessive trait among the parents.

The nub of Lilienfeld's argument is that traits obviously not determined by a single pair of alleles in homozygous state can display a binomial distribution as far as parental mating type is concerned. This is illustrated by the calculations for the trait, "attendance of medical school," shown in Table IV.

374. Problems involved in the interpretation of data on familial aggregation for common diseases such as cancer and psychoses were discussed by Haenszel.

375. Lenz provided a critique of parental age and birth order investigations. Among other matters he pointed out the following.

"Comparison of the birth rank of propositi with their normal siblings from incomplete sibships produces a systematic error due to complete ascertainment of sibs born before the propositi and incomplete ascertainment of those born after the propositi.

"When propositi from complete sibships are compared with their siblings it has to be taken into account that the probability of ascertainment of a sibship is proportional to the number of its [affected] members."

376. Reed critically examined the definition of relative genetic fitness (W) of individuals with specific genetic traits, that is, questions of what to measure and what to use as a reference population. He has shown that unaffected siblings are not an appropriate standard of comparison for reproductive fitness with regard to dominant traits (see ¶582); in Huntington's chorea, reproductive fitness of unaffected siblings, in terms of average number of children, is reduced when compared with the general population. Probably, decisions on family size are influenced by knowledge of the presence of recognizably hereditary disease in the family. Reed suggested that a factor which must not be omitted from consideration in fitness estimates is parental age distribution (age at the birth of their children).

377. Lowry and Shultz discussed the problem of testing association of metric traits and marker genes. Although specific attention was directed to metric traits of domestic animals, such as egg production in hens, the discussion is presumably pertinent to metric characters in man, such as blood pressure level.

Smith commented on the statistical methods used in linkage investigations.

378. Biochemical methods. Markert and Møller pointed out the usefulness of Smithies' starch gel electrophoresis technique for demonstration of differences in enzyme proteins which have identical substrate specificity. "Isozyme" was the term they suggested for the members of such families of enzymes; they call the starch strip containing the visualized enzymes a "zymogram." Conventional histochemical staining techniques were used to demonstrate several enzymes (Markert and Hunter)—esterases, phosphatases, tyrosinases, peroxidases, and dehydrogenases. The potentialities of the method are probably considerable, especially for demonstrating polymorphic characteristics. Panek discussed the detection of enzymes by paper chromatography.

Ghadimi and Shwachman described a rapid, simple, and inexpensive screening test for aminoaciduria.

379. Others. Newcombe and colleagues at the laboratories of Atomic Energy of Canada at Chalk River, Ontario, have been developing methods for collating the routine vital statistics data so that information of genetic significance can be derived. Digital computers are being adapted to this application.

Considerable success has accompanied the initial explorations. Since the raw data are routinely collected for administrative purposes, some additional expense to put them in a form susceptible to meaningful analysis in genetic terms should be justified.

Schachter of the Office of Vital Statistics was quoted (Furman) as stating that the vital statistics system offers an efficient way to get accurate data on the outcome of pregnancies, the frequency of malformations evident at birth, and certain other matters. A national tabulation of malformations at birth will be started in 1960 by the Office of Vital Statistics.

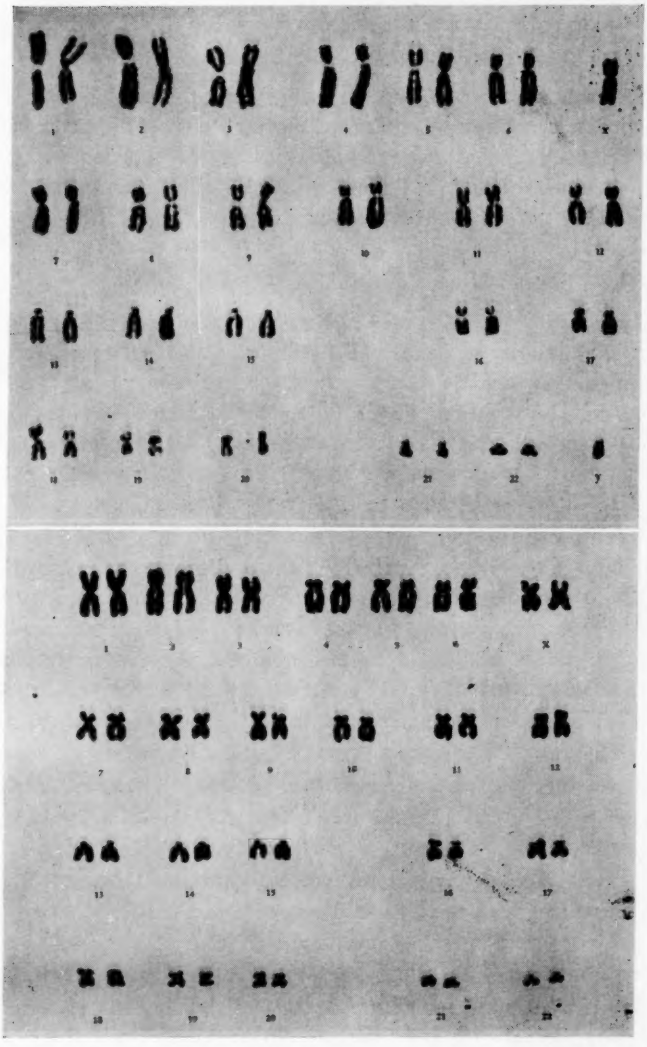
VI. CYTOGENETICS IN MAN

380. Techniques of nuclear sexing were discussed and illustrated by Ashley. Guard described a technique using Biebrich scarlet and fast green and Cuadrillero used silver impregnation. By this method sex chromatin was demonstrable in 97 to 98 per cent of exfoliated vaginal epithelial cells. Olmstead applied the principles of sequential analysis to the assignment of chromosomal sex by means of the nuclear chromatin in buccal smears. The advantage consisted of a reduction (about 75 per cent) in the number of cells which had to be counted to arrive at a confident decision.

Barr of the University of Western Ontario, discoverer of sexual dimorphism in intermitotic nuclei, reviewed the subject of sex chromatin and sex phenotype in man. There are many useful features, although the flurry of discoveries on the role of aneuploidy in developmental errors and on the chromosomal basis of sex differentiation in man render some of the discussion outdated. ". . . The requirement of a masculinizing evocator of testicular origin to counteract a tendency of all embryos to feminize is a keystone in current concepts of the pathogenesis of congenital errors of sex development." The masculinizing evocator seems to have a local action on adjacent tissues. "Wolffian ducts (primordia of epididymides, vasa deferentia, and seminal vesicles) and Müllerian ducts (primordia of Fallopian tubes, uterus, and vagina) are both present when gonadal differentiation begins, and the external genitalia are also in a bipotential state." Regardless of the sex of the donor rat embryo, the Müllerian ducts persist and grow in vitro whereas the Wolffian ducts regress. This suggests that the inherent tendency to feminization is determined genetically and not by maternal estrogens.

In a follow-up note on the article just referred to, Barr pointed out that Ohno and colleagues can find pairing of the X chromosomes of the mouse only in epithelial cells of the Graafian follicles and in the mammary gland—not in other somatic tissues. Furthermore, Kosin and Ishizaki showed that in domestic fowl the female shows sex chromatin. Since in birds the female is the heterogametic sex, the basis for the sex chromatin cannot be the heterochromatic parts of *two* sex chromosomes. Furthermore, Ohno and colleagues made the startling demonstration in prophase nuclei of regenerating liver cells of female rats that one X chromosome displays positive heteropyknosis, whereas one is isopyknotic in relation to the autosomes. They suggested that the positively

A.



B.

Fig. 2.—The human metaphase chromosomes. *A*, Male. *B*, Female. (Preparations by M. A. Ferguson-Smith and A. W. Johnston.)

heteropyknotic X chromosome may be of paternal origin and that it solely may be concerned in the formation of the sex chromatin body in the female interphase nucleus.

Sexual dimorphism of intermitotic nuclei (as shown by the Barr test and other techniques) is present in primates, carnivores, marsupials, and artiodactyls

VOL. 12 196

(e.g., cattle), but not in the rabbit or rodents. There are, however, exceptions to this statement; the motor neurons of female rats and hamsters show sex chromatin and the female rabbit shows "drumsticks" of the leukocyte nuclei. Meier demonstrated sexual dimorphism in the white cells of the rat—a drumstick in the polymorphonuclear leukocytes of females and a planoconvex body in the lymphocytes. However, these were sparse, so that their demonstration was time consuming and fraught with artefacts.

380a. In Formosa, Chang studied the ovaries of 10 Chinese fetuses. Mitotic figures of oogonia were identified and analyzed. He concluded that the diploid number in human oogonia is 48, but his plates were *not* of sufficient quality to inspire the reader's confidence in the conclusion.

Chu and Giles of Yale studied the chromosomes of 34 normal human subjects as found in tissue cultures of somatic cells. In all, the diploid number was 46. On the basis of relative chromosome lengths and arm indices, an idiogram of the human karyotype was constructed. Each pair of chromosomes was designated by a number. Seven subgroups were identified. (There is risk of great confusion unless a uniform numbering system is employed. Slightly different systems are represented in the idiograms of Ford and associates, Jacobs and co-workers, and Tjio and Puck [¶ 68].) Two pairs of autosomes (14 and 21, in the numerology of these authors) have satellites on their shorter arms. The fact that there are two pairs of nucleoli, one large and one small pair, in somatic nuclei supports the view that the autosomes with satellites are nucleolus-organizing chromosomes.

The method used by Ford in the study of chromosomes consists of short-term cell culture of sternal marrow, treatment with colchicine to stop mitosis at metaphase, and Feulgen staining of squash preparations. The chromosomes are drawn by use of the camera lucida or are cut out of large photographs and arranged into groups by size and kinetochore position. (Fig. 2.) Lejeune and other groups have used fibroblast cultures from fascia lata, growing them on microscope slides. Yet a third method is a modification of that of Osgood and colleagues (1955) using peripheral blood (Hungerford and co-workers). The cell that survives is presumably a monocyte. Studies by Nakanishi and associates with human amnion cells indicate the changes in chromosome number which occur after a few weeks of culture. Puck has indicated that polyploidy can be kept at a minimum or avoided entirely by his techniques.

The recent improvements in cytologic technique have permitted direct study of chromosomes in relation to congenital disorders in man. At least three major advances in the cytogenetics of human disease were made:

381. I. In *Mongoloid idiocy* (¶591), an additional autosomal chromosome, one of the smallest ones with subterminal kinetochore and with satellites, was found by Lejeune and his colleagues in Paris. This finding was confirmed by Jacobs and coauthors and also by Böök, Fraccaro, and Lindsten. It is probably not presumptuous to consider the extra chromosome—or rather the trisomic state—as the "cause" of Mongolism. (Fig. 3.)

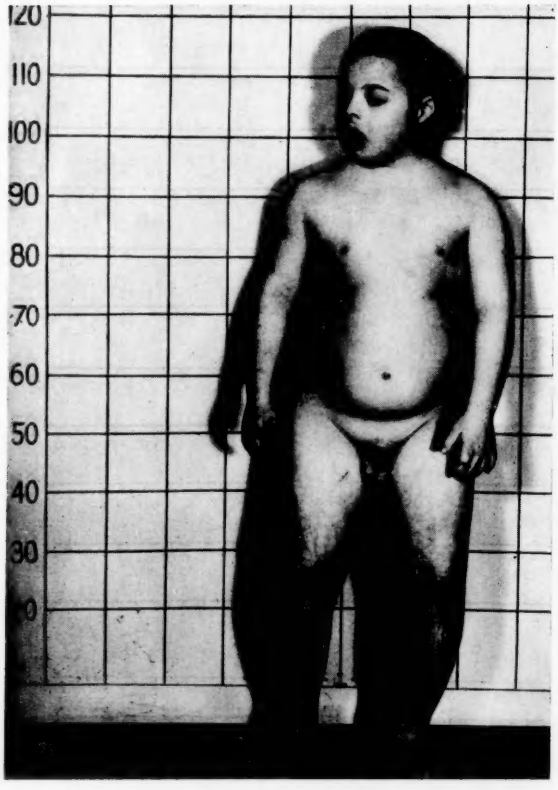


Fig. 3*A*.—O. W., a 14-year-old male Mongoloid idiot, shows short stature, characteristic eyes and facies, flat occiput, stubby hands with particularly short fifth digit, poor circulation with cutis marmorata, and loose-jointedness (in the ankles, for example).

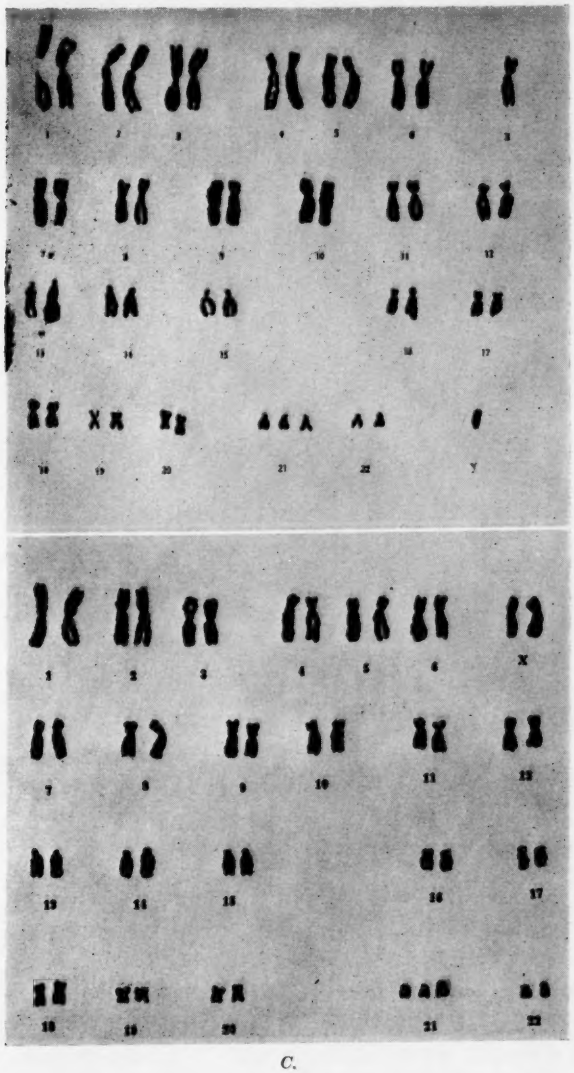
382. II. In at least 40 per cent of cases of the *Klinefelter syndrome* (¶553), there is chromatin-positive nuclear sex despite the male phenotype. The paradox suggested that genetic sex is peculiar, and therefore it became of importance to determine the sex chromosome constitution. Ford, Jacobs, and Lajtha (1958), on the basis of counts in only five cells in one case, stated that the diploid number was 46 and the sex chromosome constitution XX. Jacobs and Strong described a typical case with adequate counts and found the diploid number to be 47 with an XXY complement. Later Ford and associates described a chromatin-positive case of the Klinefelter syndrome which they thought might represent a mosaic of cells containing 46 and 47 chromosomes. The counts were as follows:

Number of chromosomes	41	42	43	44	45	46	47	48	49
Number of cells	1	0	0	2	3	13	44	1	1

In 3 other chromatin-positive cases of the Klinefelter syndrome they found 44 A+ XXY with no evidence of mosaic inheritance. (Fig. 4.)

Steinberg, in a letter to the editor of *Science* published in early 1959, suggested that complete sex reversal might be detected in the case of reversed females functioning as males by doing Barr chromatin tests on the fathers of all-girl families. Steinberg was assuming that such individuals are XX. Shortly after appearance of the letter, the true chromosomal constitution of the Klinefelter syndrome as XXY was reported. Thus, even if a person with the Klinefelter syndrome were capable of procreation, all female offspring would not be expected.

B.



C.

Fig. 3*B* and 3*C*.—*B*, The metaphase chromosomes of the male Mongoloid shown in 3*A*. *C*, The metaphase chromosomes of a female Mongoloid idiot. (Preparations by M. A. Ferguson-Smith and A. W. Johnston.)

That there are other individuals with XX sex chromosome constitution, complete sex reversal, and competence as males is both uncertain and unlikely.

A remarkable case showing the features of both the Klinefelter syndrome and Mongolism was found by Ford and colleagues to have a diploid number of 48, an XXY sex chromosome constitution, and an additional small autosomal chromosome with subterminal kinetochore.

383. III. In *the Turner syndrome*, gonadal aplasia (¶550), in which there is also an apparent discrepancy between nuclear sex and somatic appearance, the

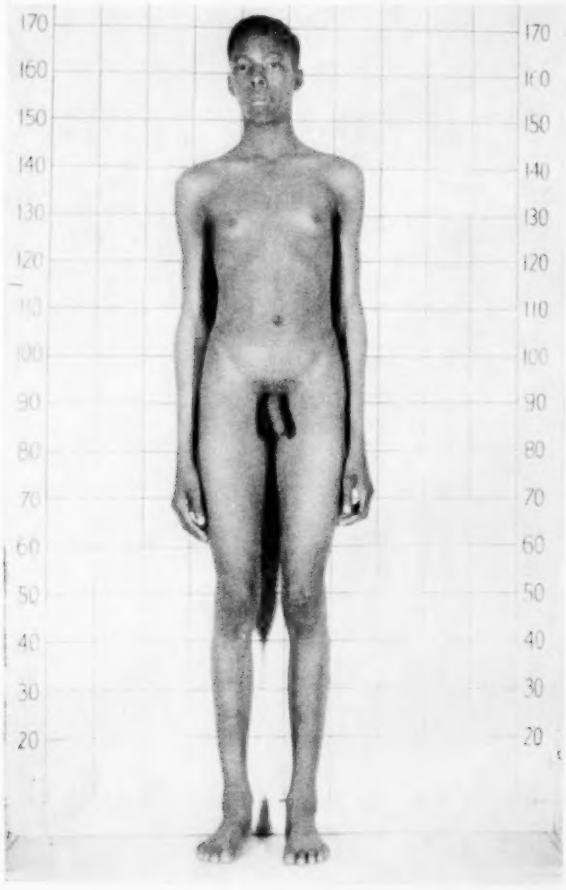


Fig. 4*A*.—Klinefelter's syndrome. J. V. D. (856375), an 18-year-old Negro male, came to the hospital because of enlarged breasts. He also demonstrates undervelopment of body hair, a penis which he considers smaller than that of his contemporaries, very small testes, and a very small prostate. The upper segment–lower segment ratio (about 0.81) is within two standard deviations of the mean for 18-year-old Negro males. He has never shaved. His libido is moderately strong. He has no difficulty in attaining erection and has heterosexual relations about once monthly. The IQ is 76. The 24-hour urinary excretion of 17-ketosteroids was reduced (9.92 mg.). At the time of biopsy the left testis was found to be little larger than a lima bean.

VOL. 12 196

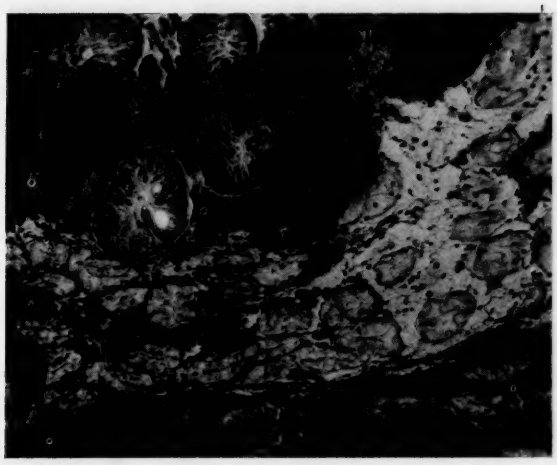


Fig. 4*B*.—Histologically, the majority of the seminiferous tubules are completely atrophic and are seen as small, shrunken, hyalinized "ghosts" (center and lower area). A few small tubules lined exclusively by Sertoli cells persist among large masses of Leydig cells (top left). No germinal cells are identified. (Hematoxylin and eosin; × 150; reduced one-third.)

diploid number was found to be 45, the sex chromosomal constitution XO (Ford and coauthors; Jacobs and Keay; Tjio, Puck, and Robinson; Fraccaro, Kaijser, and Lindsten). The absence of the Y chromosome results in the female phenotype and the presence of but one X chromosome for the "chromatin-negative" status shown by about 80 per cent of cases. The findings in this and in the Klinefelter syndrome indicate that sex determination is different in man than in the vinegar fly (¶'s 310*k*, 388). XO is male (sterile, but otherwise normal) in Drosophila; XXY is a fertile female. (Fig. 5.)

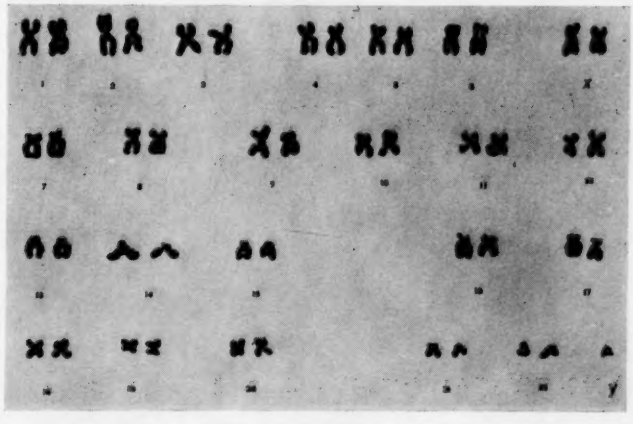


Fig. 4*C*.—The metaphase chromosomes in Klinefelter's syndrome. (Preparation by M. A. Ferguson-Smith and A. W. Johnston.)

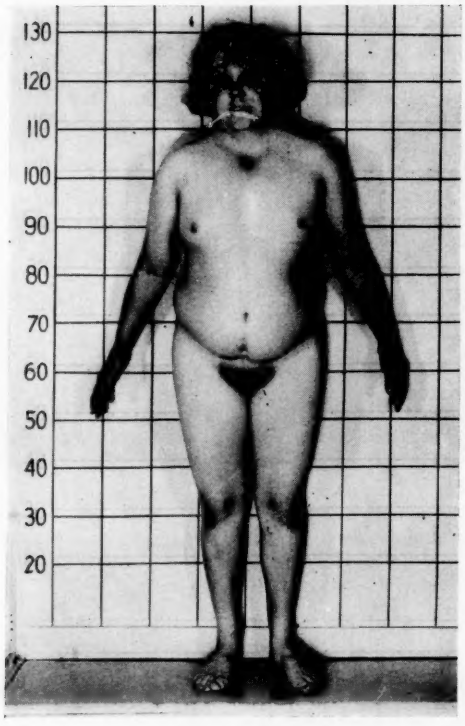


Fig. 5*A*.—Turner's syndrome (gonadal aplasia). Now 37 years old, M. H. (270068) demonstrates classic features of gonadal aplasia: short stature, low-set ears, hypoplasia of the jaws, web neck, shield-like chest with wise-set nipples, and coarctation of the aorta (note scar of operation for resection of same). Laparotomy revealed only fibrous streaks in the position of the ovaries.

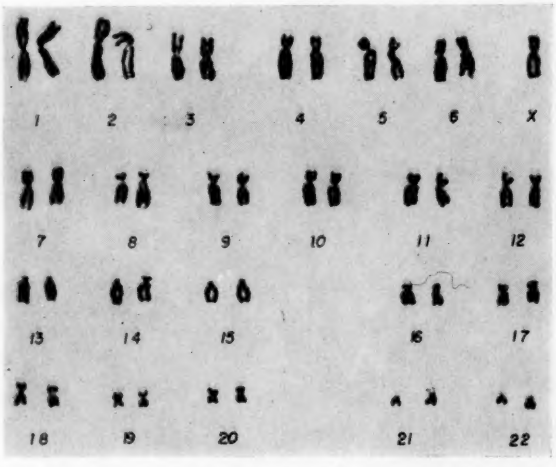


Fig. 5*B*.—The metaphase chromosomes in Turner's syndrome. (Preparation by M. A. Ferguson-Smith and A. W. Johnston.)

VOL. 12 196

384. Nondisjunction. The aneuploid states represented by the three disorders just listed are thought to represent the results of nondisjunction occurring either in meiosis or in the first mitotic cleavage of the zygote (Fig. 6). Nondisjunction has been studied in considerable detail in lower forms. In Drosophila it has been found that this accident of gametogenesis is more likely to occur in older individuals (Mottram: J. Exper. Biol. 7:370, 1930). This observation is of particular interest in connection with the well-known "maternal age effect" in Mongolism—the increased empirical risk which older mothers run of having Mongoloid children. (Manipulation of the environment, such as increased carbon dioxide, also increases the rate of nondisjunction.)

Other conditions with a parental age effect (Penrose: Mod. Prob. Ophth. 1:501, 1956), such as achondroplasia and acrocephalosyndactyly* (both of which show a paternal age effect), were of interest to study. As indicated below (¶386), no abnormality has been detected in these conditions.

Nowakowski, Lenz, and Parada found defective color vision in 3 of 34 chromatin-positive cases of the Klinefelter syndrome. The finding was thought to be inconsistent with genetic femaleness. However, the most recent information on the XXY constitution of these cases was unknown at the time the article was written. Polani and coauthors (1958) had found no color blindness in 55 (figure later brought to 72 cases). Stern proposed an explanation for cases of color blindness. When the mother is color blind, as was the case in one, nondisjunction of the 2 X chromosomes provides adequate explanation. In those cases in which both parents had normal color vision, Stern proposed that crossing over among the four chromatids present in the first stage of meiosis followed by "equational" nondisjunction is an explanation. If the explanation is correct, it would suggest that most cases of the Klinefelter syndrome result from nondisjunction in the mother and that the locus for color blindness lies at a sufficient distance from the kinetochore (centromere) of the X chromosome to permit crossing over.

Since direct proof of nondisjunction as the basis of aneuploidy in Mongolism and in the Klinefelter and Turner syndromes is difficult to obtain, it is worth while to exclude alternative explanations such as a chromosomal aberration in a parent. In the mouse XO females are occasionally fertile (Welshons and Russell). Jacobs and Strong found a normal chromosome complement in both parents of a patient with the Klinefelter syndrome. Similarly Fraccaro, Kaijser, and Lindsten found no chromosomal abnormality in the parents of a patient with gonadal aplasia.

385. Other sex aberrations. Jacobs and colleagues described an XXX human corresponding to the "superfemale" in Drosophila. (Stern commented on the inappropriateness of the term "superfemale" and suggested "metafemale" as a substitute. Jacobs and colleagues defended the term "superfemale."†) The subject, a 35-year-old female, had been born of a 41-year-old mother. The father

*Kluge described a patient with Apert's syndrome born of a 44-year-old mother and a 56-year-old father.

†Use of the designation "triple X syndrome" (see Fig. 6) avoids this controversy.

was probably 40 years old when she was born. Menstruation had been highly irregular and infrequent. Laparotomy showed ovaries which grossly looked postmenopausal and microscopically showed deficient follicle formation. Of 63 cells, 51 showed 47 chromosomes. The extra chromosome appeared to be in the X group. The buccal smear showed one chromatin mass in 57 per cent and

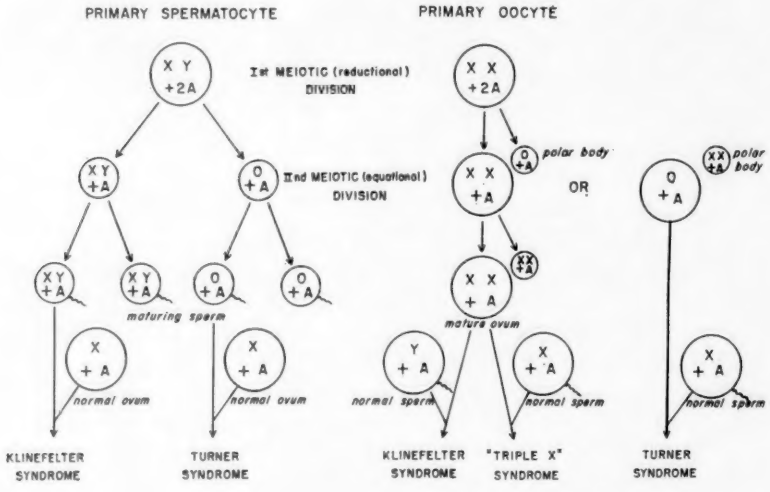


Fig. 6*A*.—Schematic representation of meiotic nondisjunction of the sex chromosomes.

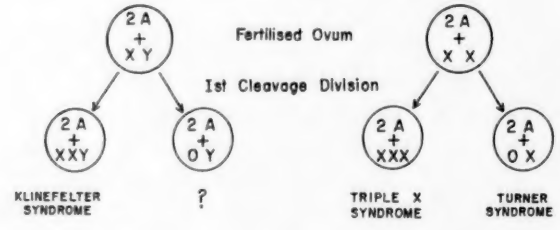


Fig. 6*B*.—Schematic representation of mitotic nondisjunction of the sex chromosomes. Use of the designation "triple × syndrome" avoids the controversy over the term "superfemale."

two chromatin masses in 14 per cent more cells. Double chromatin masses represent a useful way to screen for this condition. The mother had 46 chromosomes (XX).

Hungerford and colleagues studied a true hermaphrodite. The external genitalia were male. There were a right ovotestis and a left testis, however, and pronounced breast development. The subject was chromatin positive in tissues from several parts of the body including both sides. They concluded on the basis of cultures of peripheral blood that the sex karyotype was XX. The possibility of mosaic inheritance (e.g., XX/XXY) with survival of only XX cells in the culture could not be excluded. Harnden and Armstrong described a similar case

with left ovary and right ovotestis in which the diploid number was 46, with XX sex chromosomes.

Harnden and Stewart reported a case of what they called "pure gonadal dysgenesis." The patient was a tall, eunuchoid female with primary amenorrhea, no breast development, and scanty axillary and pubic hair. The external genitalia were normal, and there was a palpable uterus but no palpable gonads. Nuclear sex was chromatin negative and the urinary excretion of FSH was increased. The diploid number was found to be 46, with an XY sex chromosome constitution. Without a laparotomy, it would seem unwise to exclude the possibility of male pseudohermaphroditism in this case.

It will be recalled that Walton (Acta genet. 7:318, 1957) described a case of the sex-linked recessive trait Duchenne muscular dystrophy in a patient with gonadal aplasia. With demonstration of XO sex chromosome constitution in such cases, Walton's report now has its full explanation. Nilsson and colleagues found hemophilia A in a 16-month-old phenotypic female. The mother and maternal grandmother were, by internal evidence, carriers—a brother and 2 male cousins were hemophiliacs. Chromosome studies revealed 46 chromosomes and a probable XY sex chromatin pattern. The "girl" may be hermaphroditic or possibly an example of the syndrome of testicular feminization (¶552). The authors suggested that such a mechanism as this may explain the occurrence of hemophilia A in a female with negative family history reported by Quick and Hussey (1958).

386. Congenital malformations. Turpin and colleagues reported what may be the first translocation in man. In a 4½-year-old boy with "polydysspondylie" (absence of third left dorsal hemivertebra and third left rib, fusion of C_3 and C_4 vertebrae, spina bifida occulta at C_5, left hemilumbarization of S_1, calcification of the interclinoid ligament, IQ 86, and generally retarded development), the Paris group found the diploid number to be 45. The absent chromosome was one of the small subterminals. In addition one of the large telecentric chromosomes had much larger short arms than it should have. Translocation with elimination of the centromeric fragment of the small chromosome seems possible.

The search for qualitative or quantitative aberrations of the chromosomes as the basis of other congenital abnormalities is now on. It is noteworthy that it is one of the smallest chromosomes which is involved in Mongolism; duplication of a large chromosome might be expected to be lethal. It is to be noted further that Ford's patient with Mongolism had the Klinefelter syndrome (q.v.); two nondisjunctions were present. It will be of interest to determine the frequency of the Klinefelter syndrome in Mongoloid idiots.

Various disorders in which the chromosomes have been studied with no abnormality detected include the following:

Tjio, Puck, and Robinson—Marfan syndrome, phenylketonuria, female pseudohermaphroditism, and Gaucher's disease

Jacobs and associates (Lancet 1:160, 1960)—Achondroplasia, epiloia, microcephaly, juvenile amaurotic idiocy, chromatin-positive gonadal

aplasia, neurofibromatosis, and Albright's polyostotic fibrous dysplasia

Harnden, Briggs, and Stewart—Anencephaly (¶428)

Turpin and colleagues—Epiloia, achondroplasia, anencephaly (¶428), and hypopituitary dwarfism

Fraccaro, Kaijser, and Lindsten—Parents of patients with gonadal aplasia

Böök, Fraccaro, and Lindsten (including personal communication)—Juvenile amaurotic idiocy, Laurence-Moon-Biedl syndrome, achondroplasia, osteogenesis imperfecta, acrocephalosyndactyly, schizophrenia, chondrodystrophia calcificans congenita, and epidermolysis bullosa

Böök and Santesson (Personal communication)—Marfan syndrome, tuberous sclerosis, acrocephalosyndactyly, and schizophrenia

Ford—Spastic paraplegia and hypopituitary dwarfism

Harnden—Hydatidiform mole

Progeria is another condition which might repay chromosomal studies. Like Mongolism, progeria is a generalized disorder which reproduces itself with amazing fidelity in case after case. Although progeria has features which suggest a consistent genetic basis, more than one case has apparently never been found in the same sibship. Album reported on a patient with progeria who was 12 years old in 1958; however, unfortunately, the patient died of coronary atherosclerosis (Album: personal communication) before chromosomal studies could be arranged. (The condition may be a rare dominant mutation rather than a chromosomal aberration.)

387. Neoplasms. Baikie and associates studied in detail a case of monocytic leukemia in an aleukemic phase. The skin chromosome number was 2n = 46. The first three marrow chromosome counts had a modal number of 48 with ring chromosomes and fragments. Just before death the count was 47. Of other cases, 2 of acute leukemia showed 46 chromosomes, but with an abnormal chromosome which may have represented a translocation; in one case of acute leukemia the count was 46-50, with no structural abnormality; in 7 (one of acute leukemia, 5 of chronic myeloid leukemia, and one of chronic lymphatic leukemia) the karyotype seemed normal, as was also the case in 2 instances of myelomatosis. The findings suggested that the cause of chronic leukemia is different from that of acute leukemia. Ford and Mole, on the other hand, suggested that the observed difference may not be a fundamental one. Because of differential growth rates, one may be likely to study a larger proportion of the normal marrow cells in cases of chronic leukemia.

The chromosomes of an ovarian teratoma were studied by Galton and Benirischke. Material from the tumor was cultured in vitro and about 100 metaphase plates observed. Four plates only were suitable for accurate counting and charting, and the diploid number was 46 in each case. The analysis was

interpreted as showing a normal female chromosome complement. The authors believe that these mitoses are derived from the tumor tissue rather than the supporting cells but offer little evidence for this belief (see ¶570).

388. An important result of the recent cytogenetic studies is the demonstration that sex determination in man (and the mouse) is different from that in Drosophila and that the Y chromosome is not a "dummy" but rather determines the male phenotype. From birth to adulthood, skeletal maturation in girls proceeds at a faster rate than in boys. Tanner and colleagues found that in 27 children with chromatin-positive Klinefelter syndrome (XXY), skeletal age corresponded with that of a control group of normal boys, whereas in 40 children with "chromatin-negative" Turner syndrome, skeletal age corresponded with that of a control group of normal girls. It was suggested that genes on the Y chromosome are responsible for the sex dimorphism in skeletal maturation. The long-leggedness in the Klinefelter syndrome is not due to delay in epiphyseal fusion but rather to a fundamental difference in growth rate. Possibly the "double dose" of X chromosomes is responsible for the latter.

Analysis of the effects of trisomy, that is, the developmental genetics of Mongolism, the Klinefelter syndrome, metafemale state, etc., will be of great interest and importance. However, discouraging experience in lower forms which are more favorable for study, e.g., Jimsen weed studied by Blakeslee, suggests that such analysis will not be easy.

389. A chromosome newsletter, comparable to the virus newsletter, has been initiated in Puck's laboratory to make new information in this field rapidly available.

VII. BIOCHEMICAL GENETICS

With a few exceptions, the subject matter of this section is that of inborn errors of metabolism in the original Garrodian sense. In recent years biochemical genetics has come to encompass much more than merely the genetics of enzyme systems and intermediary metabolism. The hemoglobinopathic conditions (¶472 ff.), the blood group substances (¶491 ff.), and polymorphic traits (¶351 ff.) such as the haptoglobins, β globulins, or isoniazid metabolism are legitimately a part of biochemical genetics in the broader sense. Biochemical defects in active transport systems—in the renal tubule (e.g., ¶400), the gastrointestinal mucosa (e.g., ¶405), or the tissue cells (e.g., ¶397)—underlie some heritable disorders. It is the ultimate ambition of medical genetics to explain all genetic disease in biochemical terms. Even the chemical nature of the genetic material is properly considered to be within the purview of biochemical genetics.

390. General. Markert and Møller demonstrated, by a technique combining starch gel electrophoresis and conventional histochemical staining methods (see ¶378), that enzymes with similar or identical substrate specificity are different in different species, at different stages in development, and in different tissues

of the same individual. Enzymes which catalyze the same reaction but have differing physical, serologic, or chemical properties are called "isozymes" by Markert. The isozyme pattern differs from species to species and probably, to some extent, from individual to individual. The nature of the genetic control awaits elucidation.

The difference of isozymes in different organs of the same individual may have its basis not in the enzymatically specific part of the molecule, but rather in the part which is the handle by which the cell holds onto the enzyme. One should not think of cells as merely bags of free-floating enzymes. Green and Järnefelt stated the following: "Enzymes do not operate in vivo as freely diffusible molecules. . . . The enzyme activity of composite systems may not always be demonstrated as the sum of the activities of the individual enzymes contained therein."

Jehle discussed the problem of amino acid sequence selection in protein synthesis—a matter central to gene action. Christensen discussed active transport systems with special reference to the amino acids.

In reviewing the last 50 years of medical genetics, Snyder gave the most prominent place to biochemical genetics.

VOL. 12 1960

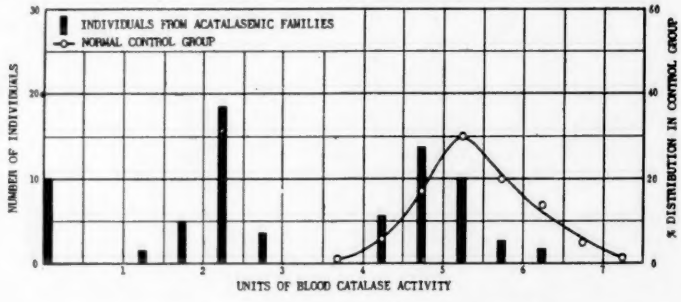

INDIVIDUALS FROM ACATALASEMIC FAMILIES
NORMAL CONTROL GROUP
NUMBER OF INDIVIDUALS
% DISTRIBUTION IN CONTROL GROUP
UNITS OF BLOOD CATALASE ACTIVITY

Fig. 7.—Acatalasemia. Distribution of catalase values from members of five acatalasemia families and comparison with a percentage distribution curve of values from a normal control group. (From Nishimura, E. T., and Coauthors: Science 130:133, 1959.)

391. Acatalasemia. Takahara and colleagues in Japan (1949, 1952) described a disorder occurring in multiple siblings, manifested by progressive gangrenous gingivitis and absence of catalase activity in the peripheral blood. Thirty-eight cases in seventeen families have been discovered. In sixteen of the families there was consanguinity. In fourteen families, 2 or more siblings were affected. The trait seems to be transmitted as a simple, autosomal recessive one.

In a study reported by Nishimura and colleagues, including Takahara, catalase activity of the blood was determined in a population sample and in acatalasemic families (Fig. 7). The parents show hypocatalasemia, the patients show acatalasemia, and unaffected siblings show either hypocatalasemia or normocatalasemia. Here is a beautiful demonstration of the heterozygous carrier state.

392. Agammaglobulinemia. Henley reviewed the subject and reported brothers with agammaglobulinemia. Three maternal uncles had been affected. (See ¶527.)

The case of Slavin and colleagues, historic because it concerned perhaps the first patient in whom complete absence of γ globulin was recognized (in 1942), may not have been hereditary. Sporadic bacterial infections were frequent in infancy and early childhood, but the patient lived to the age of 29 years.

393. Albinism. As part of a symposium, Fitzpatrick and Szabo and also Lerner and Case gave comprehensive discussions of chemical and cytologic aspects of pigmentation.

394. Alkaptonuria. Milch did an extensive study of a large number of persons in eight generations of seven highly interrelated families residing in the Dominican Republic. A total of 47 cases of alkaptonuria were discovered. The study was prompted by the fact that the family reported by Pieter (1925) to suggest dominant inheritance and that reported by Milch and Milch (1957) were both derived from the Dominican Republic. Milch confirmed suspicions that the two reports concerned related individuals. Furthermore, the important conclusion resulted that the pattern of inheritance is consistent with simple autosomal recessive transmission. The "direct transmission" was probably due to mating of homozygotes with heterozygotes, a probability increased by inbreeding. Pieter's pedigree is frequently cited as evidence of a dominant form of the disease (see ¶'s 302, 311).

Zöllner published a portrait, and brief statement of the work on alkaptonuria, of Otto Neubauer (1874-1957).

Hatch referred to the tragic case of alkaptonuria in which an eye was removed for suspected uveal melanoma; the other eye had previously been removed after trauma.

Alkaptonuric arthropathy was discussed by Cervenansky, Sitaj, and Urbanek.

395. Analbuminemia. In 1954 Vennhold and colleagues of Tübingen, Germany, found a brother and sister with analbuminemia but surprisingly few symptoms. The globulins were somewhat increased and serum cholesterol was elevated. Blood pressure was low and the sedimentation rate elevated. Bennhold and Kallee studied the half-life of labeled and unlabeled albumin infused into a patient with analbuminemia. No difference was found in the two preparations, which suggests that *properly prepared* labeled albumin can be used in metabolic studies.

Using an immunologic method, Lohss and Kallee demonstrated that albumin was either absent or present in amounts less than 0.01 Gm. per cent. The presence of a small amount of albumin could account for the failure of the patients to develop hypersensitivity to infused albumin.

396. Arginosuccinuria. The abnormal amino acid found by Allan and colleagues (¶246) in the urine of 2 imbecile siblings is an intermediate in urea formation by the liver. Sporn and coauthors showed that the brain can also form urea. A defect in this function of the brain in the affected persons may account for the mental retardation and for the fact that arginosuccinic acid was present in two to three times higher concentration in the spinal fluid than in the plasma.

397. Bilirubinemia (Arias). Gradually, several varieties of hereditary bilirubinemia are being sorted out: (1) An enzymatic defect in glucuronide formation (involving glucuronyl transferase) has been found in severe congenital, nonhemolytic jaundice (Crigler-Najjar syndrome), comparable to the defect in the Gunn rats (Axelrod, Schmid, and Hammaker, 1957). (2) In the Dubin-Johnson syndrome, a pigment occurs in the liver cells; "direct" bilirubin in the serum suggests that conjugation of bilirubin occurs but that a defect in subsequent excretion exists. (3) In a group of cases which would satisfy the usual criteria for Gilbert's constitutional hepatic dysfunction, Schmid and Hammaker could find no defect in the formation of a glucuronide of N-acetyl-*p*-aminophenol (NAPA). Although alternative possibilities were discussed, the authors favored the view that the primary defect may not involve the glucuronide-forming enzyme system but rather the transport of bilirubin from plasma to the site of conjugation. (4) In cases studied by Rotor and colleagues (1948) and by others, direct bilirubin was present in the serum, no pigment was found in the liver cells, and the extrahepatic biliary tree was patent. Schiff, Billing, and Oikawa described sisters with this type of familial, nonhemolytic jaundice and suggested that the defect involves the excretion of bilirubin glucuronide. There was Bromsulphalein retention.

Childs and colleagues demonstrated impairment of glucuronide conjugation of certain test substances in the presumed heterozygotes of two families affected by familial, nonhemolytic jaundice of the grave type described by Crigler and Najjar (1952).

Benign familial icterus was described in a father and 2 sons by Fox. The same condition—constitutional hepatic dysfunction (Gilbert's disease)—was discussed on the basis of 116 cases at the Mayo Clinic (Foulk and associates). Elevation of indirectly reacting bilirubin in the serum is the main finding. The hereditary nature of Gilbert's disease has been assumed in some of the designations for the syndrome. Alwall and associates (1946) suggested that it is a Mendelian autosomal dominant trait with incomplete penetrance. No detailed family studies were undertaken by Foulk and associates. They suggest that the primary defect is a partial deficiency in glucuronyl transferase such that transfer of glucuronic acid from uridine diphosphate glucuronic acid to bilirubin is imperfect. They suggest further that the Crigler-Najjar syndrome may be merely a more severe form of the same defect. They also discuss the Dubin-Johnson syndrome in which direct bulirubin is elevated, Bromsulphalein excretion is impaired, and characteristic biopsy changes are found.

Blanc and Johnson report that the clinicopathologic syndrome of kernicterus in rats with a hereditary defect in liver glucuronyl transferase activity (the Gunn

VOL. 12 1960

rat) is similar to that in human kernicterus. The earliest detectable change in ganglion cells of the brain was associated with the presence of apparently unconjugated bilirubin, which seems, therefore, to be the toxic agent.

Israels, Suderman, and Ritzmann described yet another form of hereditary hyperbilirubinemia they termed "shunt hyperbilirubinemia." In this form the excess bilirubin appears to be derived from a source other than circulating erythrocytes, through an alternate pathway of bilirubin production. Clinical manifestations—jaundice and splenomegaly—have their onset in the second decade. They found 4 cases in two Mennonite families living in Canada. Three of the patients were siblings. Since Krefeld was a German center of Mennonites, the authors speculated that these patients might have a remote relationship to those described by Kalk (1955) of Kassel, which is not far from Krefeld.

398. Cystathioninuria. In a survey of about 1,000 low-grade mental defectives, Harris and colleagues found an abnormal amino acid in the urine of one, an elderly imbecile. Cystathionine, not previously identified in human urine, was excreted at the rate of about 500 mg. per day. Other amino acids were normal. Cystathionine is an intermediate in the breakdown of methionine to cysteine. A defect in the enzyme normally concerned in cleavage of cystathionine to cysteine and homoserine was postulated. A brother and a nephew, normal clinically, showed a slight increase in urinary excretion of the amino acid; they may be heterozygous for a gene present in homozygous state in the imbecile. Tallan's discovery of cystathionine in normal brain tissue (J. Biol. Chem., 1958) is probably relevant.

399. Cystinosis. Garron gave a case report, largely from the ophthalmologic point of view, of a white girl, 9 years old at the time of death. Features were dwarfism, renal rickets, and deposition of cystine in many tissues—cornea (demonstrated by slit lamp), conjunctiva (demonstrated by biopsy), and (by autopsy) the liver, kidneys, bone marrow, spleen, adrenals, lymph nodes, and several parts of the eye. (See also Capper's report.)

400. Cystinuria. Smith, Kolb, and Harper gave a general discussion. Berry described cystinuria in a group of siblings, offspring of an incestuous mating, some of whom were also affected by mental retardation and an atypical form of osteogenesis imperfecta without blue sclerae or deafness. The occurrence of independent, recessively inherited traits seems likely.

Winer reviewed the practical value and the techniques for analysis of urinary calculi. Two methods for identifying cystine stones were mentioned:

a. Powdered stone, 1 drop NH_4OH, and 1 drop 5 per cent NaCN; after 5 minutes, add 2 to 3 drops of 5 per cent sodium nitroprusside. Result: beet red color which on standing may fade to orange red.

b. Char stone over flame. Result: hydrogen sulfide odor.

Boström and Tottie screened urine specimens from 7,793 first grade school children in Stockholm and found 3 with cystinuria and 14 with "incomplete cystinuria." The 95 per cent confidence limits for the prevalence of cystinuria

were 1 to 891 and 1 to 12,569. Cystinuria was defined as the excretion of cystine, lysine, arginine, and ornithine; these individuals are presumably homozygous. Incomplete cystinuria was defined as the excretion of only cystine and lysine; these persons are presumably heterozygous. Boström analyzed prognosis in

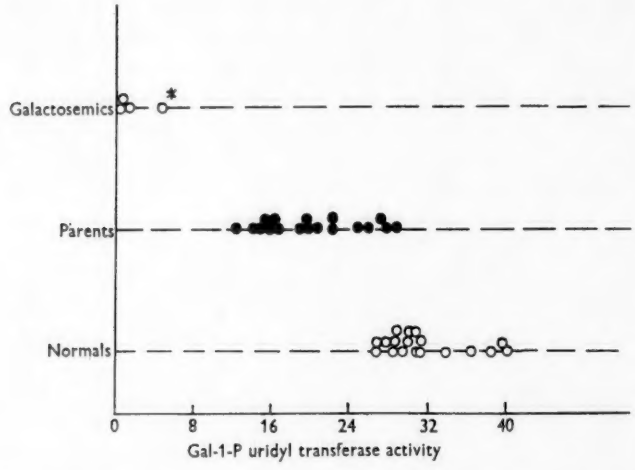


Fig. 8.—Galactosemia. The asterisk indicates a patient in whom the determination was performed after transfusion. (From Kirkman, H. N., and Bynum, E.: Ann. Human Genet. 23:117, 1959.)

homozygous cystinuria on the basis of 66 cases in Sweden. He divided the cases into those ascertained because of the development of kidney stone (n = 40) and those ascertained by screening (n = 26). On the basis of 16 primary cases which had been fatal, prognosis was judged to be worse in men. Twelve of the deceased patients were men, and the average age at death in the 5 men who died of kidney disease was 36.8 years. All 4 women lived to an advanced age. In the cases ascertained by screening, the frequency of stone was as follows: by 26.0 years, 4/9; by 33.2 years, 10/19; and by 57.1 years, 8/9.

401. Galactosemia (Isselbacher). Van Geffel and colleagues pointed out that aminoaciduria may persist for some days after withdrawal of galactose from the diet and after disappearance of galactosuria. They also indicated that there is aminoacidemia as well as aminoaciduria and that the aminoaciduria is an "overflow" phenomenon as well as the result of pure renotubular factors. One would presume that the aminoacidemia is a result of disturbance of liver function. Its persistence for a time after disappearance of galactosemia is not surprising.

Collipp and Donnell described galactosemia present with gangrene in an infant. Neonatal gangrene on this basis has been described in other cases of galactosemia. The precise mechanism is not clear; apparently multiple, small venous and capillary thromboses are involved.

Lerman observed a deficiency of the enzyme galactose-1-phosphate uridyl transferase in the cataractous lenses removed from a galactosemic infant. (Normally the enzyme is present in the lens in amounts comparable to that in the erythrocytes.) He postulated that an accumulation of galactose-1-phosphate in the lens might inhibit the metabolism of glucose, which is the main source of energy of the lens, and thereby result in cataract. He was able to show that in the rat lens, glucose-6-phosphate dehydrogenase activity is specifically inhibited by galactose-1-phosphate, both in vitro and in vivo (in animals fed galactose).

Donnell, Bergren, and Roldan studied thirteen galactosemic families. The proportion of affected siblings was consistent with autosomal recessive inheritance. The oral galactose tolerance test was found to be unsuitable for detection of individual carriers of galactosemia.

Kirkman and Bynum did assays of galactose-1-phosphate uridyl transferase activity in the blood of patients with galactosemia, parents of persons with galactosemia, and normal subjects (Fig. 8). The values for enzyme activity in the presumably heterozygous parents was intermediate between that in galactosemia and those of normal individuals. They seem to have demonstrated clearly that galactosemia is an autosomal recessive trait and that it is possible to identify the heterozygote. The control normal subjects were not described. One wonders if there may be an age and/or sex effect on enzyme level which, if taken into account, would eliminate the overlap.

Bretthauer and colleagues also described a modified method for assay of galactose-1-phosphate uridyl transferase in erythrocytes and demonstrated its use in detecting heterozygotes in the families of 3 galactosemic probands. Huang, Hugh-Jones, and Hsia likewise investigated the carrier state.

402. Glucose-6-phosphate dehydrogenase deficiency. Beutler reviewed in detail all aspects, including the genetics. Ramot and colleagues found glucose-6-phosphate dehydrogenase activity to be reduced in platelets and in leukocytes of Caucasians with the erythrocyte defect. On the other hand, Marks, Gross, and Hurwitz found the glucose-6-phosphate dehydrogenase activity of the leukocytes normal in Negroes. The basis for the difference is elucidated by the comparative study of Marks and Gross which demonstrated that there is a quantitative difference in glucose-6-phosphate dehydrogenase in Negroes and Caucasians. They suggest that "different genetic mechanisms account" for the disease in the two races.

In France, Chadoutaud described a 4-year-old male with favism. The author was obviously unfamiliar with the recent elucidation of the biochemical defect. He does, however, note that males predominantly are affected, that the disease is thought to be sex linked, and that Italian ancestry is frequent. The paternal grandmother of his patient was Italian. He referred to favism as "anaphylaxie chez des sujets prédisposés par hérédité." Venturi and colleagues studied erythrocyte enzymes in 60 members of families in which favism had occurred. They confirmed completely the enzyme basis of susceptibility (Childs and coauthors, 1958; Szeinberg and co-workers, 1958).

Kantor and Arbesman raise the question of whether favism may be more complex in its mechanisms and not merely a hereditary enzyme defect of the red cell. They insist that an immunologic mechanism has not been excluded and that the hereditary and immunologic mechanisms are not mutually exclusive. They point out that the Prausnitz-Küstner skin tests are positive for fava antigen after an attack, that favism does not occur with the first exposure to the bean, and that eosinophilia accompanies acute attacks. They succeeded in demonstrating in the serum of a patient with favism a substance in 1:480 dilution which caused the agglutination of human group O, Rh-negative red cells previously treated with tannic acid and exposed to fava bean extract.

Hartigan and Gurnett reported a case of acute favism in a 74-year-old man, without any mention of the postulated enzyme defect. This patient had a white count of 14,800 and "a normal differential count." The suggestion in the literature that cortisone may help in the acute attacks was quoted, but it was pointed out that the hemolysis is self-limited even with continued exposure and the benefit may be only symptomatic.

Paolo, Fausto, and Efisio reported on 3 patients with this defect in which chloramphenicol precipitated acute hemolytic anemia.

Zinkham found that newborn infants tested before 36 hours of age have unstable red blood cell glutathione. Three Negro infants out of 66 had reduced glucose-6-phosphate dehydrogenase activity.

Shahidi and Diamond described the glucose-6-phosphate dehydrogenase defect in 2 white male siblings with congenital, nonspherocytic, hemolytic anemia. The mother showed the same defect in mild degree. Notable was the absence of identified exposure to any injurious drugs or other substances. The pedigree was consistent with transmission as a sex-linked trait of intermediate dominance. Zinkham and Lenhard also found a deficiency of glucose-6-phosphate dehydrogenase in some cases of congenital, nonspherocytic, hemolytic anemia.

Walker and Bowman found a prevalence of 8.5 per cent of primaquine sensitivity in Moslems of Iran.

Kirkman's studies of many characteristics, both physical and enzymatic, of glucose-6-phosphate dehydrogenase from normal and primaquine-sensitive erythrocytes make it unlikely that a qualitative difference exists in the latter condition. Carson, Schrier, and Kellermeyer showed that triphosphopyridine nucleotide stabilizes glucose-6-phosphate dehydrogenase and suggested, "The key to the mechanism of primaquine hemolysis, and possibly of cellular ageing, may be related to these stabilizing processes."

The defect in the primaquine-sensitive erythrocyte may not concern in a primary way glucose-6-phosphate dehydrogenase. At least four other biochemical abnormalities have been described and all may be secondary (Schrier and colleagues): (1) low, reduced glutathione (GSH), (2) unstable GSH when falls occur in vivo and in vitro on exposure to certain chemicals, (3) increased glutathione reductase activity, and (4) increased aldolase activity.

Motulsky and his colleagues have used a rapid, simple, and seemingly dependable screening test for detecting the enzyme deficiency in males. Brilliant cresyl base is used as an indicator in a reaction which is catalyzed by the enzyme

VOL. 12 196

under test. Normal persons show decolorization in 45 to 90 minutes. Enzyme-deficient patients require 140 minutes to 29 hours. The test was positive (i.e., abnormal) in about 10 per cent of Negroes and 10 per cent of Asiatic Indians. The test was used by Motulsky to study the geographic distribution of the enzyme deficiency, particularly in the Congo and in the Mediterranean basin. The distribution suggests a selective value of the defect. Malarial parasites require glutathione for growth; for this or other reasons, enzyme-deficient subjects may be more resistant to falciparum malaria. Motulsky's experience is consistent with the sex-linked nature of the gene.

403. Di Sant'Agnese discussed five types of *glycogen storage disease* (Editorial):

Hepatic form (von Gierke's)—normal glycogen structure; defect of glucose-6-phosphatase—liver and kidneys involved predominantly

Cardiac form (generalized glycogenosis)—all tissues are affected; glycogen structure normal; enzyme defect unknown

Limit dextrinosis of Cori—liver muscle and heart involved; abnormal glycogen due to absence of debranching enzyme, amylo-1:6-glucosidase

Hepatic form leading to cirrhosis—the liver and reticuloendothelial system are involved; only one case described; abnormal glycogen structure

Muscle type—skeletal muscle affected; only one case known

Hsia and Kor determined the concentrations of glucose-6-phosphate and fructose-6-phosphate in erythrocyte hemolysates from 4 patients with von Gierke's disease, 8 parents of such patients (and therefore presumably heterozygous carriers), and 10 normal control subjects. The mean concentrations in the erythrocytes of the heterozygotes were significantly greater than in those of the controls and were of the same order of magnitude as in those of the patients.

404. Gout. Because of the impressive array of historically significant persons who suffered from gout, it has been suggested that a causal relationship between gout and human accomplishment may exist. Although dietary differences might be responsible, Orowan (1955) suggested that the development of the human cerebrum stemmed from a mutation which resulted in loss of hepatic uricase. Elevation in blood uric acid is pictured as stimulating the cerebral cortex. Haldane (1955) pointed out that the postulate requires a correlation between intelligence and blood uric acid concentration. In U. S. Army inductees, Stetten and Hearon found a low but significant positive correlation between level of serum uric acid and intelligence test scores. Kerlinger criticized their conclusions.

Gout is frequent in Filipinos, possibly as much as twenty times as frequent as in Europeans (Decker and Lane).

Zöllner advanced the idea that in gout there may be a genetic defect in amino acid metabolism such that purine metabolism "must take up the overflow."

Gutman, Yü, and Berger presented evidence for tubular secretion of urate in man but could find no defect in this mechanism in cases of gout.

A hyperuricemic effect has been observed with several agents, especially chlorothiazide, a diuretic, and its congeners (Healey and colleagues) and Pyrazinamide (Cullen and associates, 1957), an antituberculosis agent. The mechanism is presumably renal. Whether genetically gouty persons overreact is not proved. Possibly those with the genetic background for overproduction of uric acid will show exaggerated hyperuricemia with chlorothiazide administration. If so, clearer phenotypic classification for family studies might be possible. Improved phenotypic classification in family studies of gout might be achieved not only by interfering with renal excretion of uric acid by chlorothiazide, but also by the use of a provocative test with a uric acid precursor such as RNA (Nugent and Tyler) or by measurement of some other blood constituent. In the latter connection it is of interest that Mugler reported hyperoxalemia in gout.

Sorenson again demonstrated that man is incapable of uricolysis. However, the bacteria of the intestinal tract degrade uric acid and as much as 200 mg. of uric acid is excreted into the digestive tract daily in the saliva, gastric juice, and bile. Nugent and Tyler found decreased uric acid clearance and excretion in patients with gout as compared with normal persons in whom the plasma levels of uric acid comparable to those in gouty subjects had been attained by administration of uric acid precursors. Might not the impaired excretion in long-standing hyperuricemia be the result of renal damage therefrom and not the result of a primary renal defect?

405. Hartnup disease (¶101) was described in 1956 by Baron and coworkers as a "hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal aminoaciduria, and other bizarre biochemical features." The disease was named for the first affected family observed. The enzymatic defect was earlier thought possibly to concern tryptophane peroxidase (Nemeth and Nachmias, Science, 1958), which is involved in the metabolism of tryptophane to nicotinamide. The work of Milne and coauthors, however, suggests that the basic abnormality involves the active transport of amino acids across the intestine and possibly at other sites such as into liver cells. Indole compounds, which, in addition to tryptophane, are found in the urine in increased amounts, are thought to be produced by bacteria in the gut from tryptophane which is only slowly absorbed from the bowel. The findings are of great interest as a clear demonstration of a hereditary defect in intestinal absorption.

A genetic defect in an active transport system is recognized as the basis for the several types of renal tubular dysfunction such as that in cystinuria (¶400). It has been suspected that the same principle accounts for disorders with main expression at other sites. Active transport mechanisms are involved in maintaining concentration gradients across cell membranes. The findings in Hartnup disease appear to substantiate the earlier suspicions. In some forms of hyperbilirubinemia (¶397), a defect in a transport system seems to be involved. Similar defects may be present in hypokalemic and hyperkalemic familial paralysis (¶562).

VOL. 12 1960

406. Hemochromatosis. Lonergan and Robbins concluded that the Kimmelstiel-Wilson syndrome, intercapillary glomerulosclerosis, does not occur in the diabetes of hemochromatosis. The improvement of cardiac function when iron was removed by repeated venesection was described by Evans. The rarity of hypothyroidism despite heavy iron deposits in the thyroid was commented on by Williams and a case of hemochromatosis with thyrotoxicosis was described.

McAlpine described 2 brothers with hemochromatosis. Their sister, aged 61 years, had elevated serum iron. The author emphasized the importance of prophylactic venesections in relatives of patients with hemochromatosis found to have elevated serum iron. He also described 2 women, aged 53 and 63 years, with clinical hemochromatosis. He was impressed by the fact that 3 of 8 patients with hemochromatosis had duodenal ulcer.

Bothwell and colleagues studied 52 immediate relatives of 6 patients with hemochromatosis and concluded, as did Debré and co-workers (¶102), that the trait is dominant with reduced penetrance and/or variable expressivity.

In one case of hemochromatosis, penicillamine had no effect on iron excretion (Seven, Kliman, and Petersen).

407. Hyperlipidemia. In 2 siblings, males, out of a sibship of 8 from a consanguineous marriage, Bigler and coauthors found evidences of a defect in lipid metabolism distinct from idiopathic hypercholesterolemia and usual idiopathic hyperlipemia. The clinical features were hepatomegaly and retardation of both physical and mental growth. The chemical feature was an increase in the concentrations of triglycerides and phospholipids in the plasma with little increase in total cholesterol. The α_2-lipoproteins were increased primarily. In idiopathic hyperlipemia and to a lesser extent in idiopathic hypercholesterolemia, there is a decrease in α_1-lipoproteins and increase in the β-lipoproteins.

Gailitis and Schreider commented on the abdominal and coronary symptoms of hyperlipemia and the risk that patients with hyperlipemia will be mislabeled neurotic or subjected to unnecessary abdominal surgery. They make the statement: "Laboratory tests short of total lipid level determination are not adequate for the diagnosis of idiopathic hyperlipemia." Although completely definitive diagnosis requires such determinations, simple inspection of the fasting serum for lactescence does, in the experience of many, suffice for the diagnosis of most cases.

Hirschhorn and his colleagues estimated that hyperlipemia, presumably familial hyperlipemia, is present in 2 to 3 per cent of Swedish university students. Examination of the fasting serum for lactescence sufficed in the recognition of the abnormality.

Haahti, in a preliminary report, described a 33-year-old male with essential hyperlipemia and no diabetes and no thyroid or renal disease. Heparin did not produce clearing of the lipemic serum, but prompt clearing occurred when albumin and heparin were infused. Most interesting was the observation that administration of insulin produced a sustained clearing of lipemia, with a marked fall in total lipids, phospholipids, and cholesterol.

Case reports were provided by Nicolai and Levi. Family studies, twin studies, and other investigations of genetic interest were separately reported,

in a published symposium, by Adlersberg and Schaefer, Guravich, Hood, and Angervall, Epstein and colleagues, Osborne and colleagues, and Hirschhorn and colleagues.

408. Hypoglycemia. In 1956 Cochrane and colleagues separated out a variety of familial hypoglycemia which is specifically precipitated by the administration of the amino acid L-leucine. Cochrane and Moya reported other clinical observations as well as animal experiments attempting to elucidate the mechanism of the effect of leucine.

409. Hypophosphatasia. Harris and Robson studied the urinary excretion of ethanolamine phosphate in 381 relatives of 16 patients with hypophosphatasia. Of these, 81 excreted abnormal amounts of this material. Their relationship to the probands suggested that these persons are heterozygous for the rare gene which causes the full syndrome of hypophosphatasia in homozygotes. Only about 58 per cent of heterozygotes could be demonstrated by this method. The rate was not affected by age or sex. A positive sibling-sibling correlation for rate of manifestation was demonstrated in the aunts and uncles of probands. When the parent was an excreter, 18 of 56 siblings were excreters. When the parent was not an excreter, only 2 of 32 siblings were excreters. There seemed to be no parent-child correlation, which suggests that there may be more than one form of "normal" allele at this locus and that such different isoalleles in combination with the abnormal allele result in different degrees of peculiarity.

See Rathbun's discussion.

410. Hypophosphatemia. Fraser and his colleagues presented evidence suggesting that the primary defect in hypophosphatemic, vitamin D–resistant rickets is not in the kidney but may be in the bowel and concern calcium absorption. The loss of phosphate by the kidney may result from secondary hyperparathyroidism. Specifically, he demonstrated that efficient phosphate reabsorption occurred when calcium was infused intravenously.

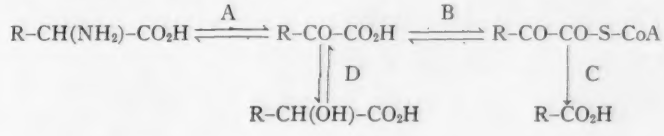
Graham, McFalls, and Winters presented data on three additional kindreds affected by sex-linked dominant familial hypophosphatemia. As in the large kindred studied earlier (¶103), penetrance for bone lesions was greatly reduced in females—to the 10 to 25 per cent range.

Dancaster and Jackson described a family with a mother, 3 sons, and a daughter affected.

411. Maple syrup urine disease. Mackenzie and Woolf reported the first case in Britain. A 4-month-old female offspring of unrelated parents had gross mental deficiency, seizures, and abnormal electroencephalogram. The urine smelled like maple syrup and contained a great excess of the α-keto acids corresponding to valine, leucine, and isoleucine and the amino acids themselves, as did also the blood, cerebrospinal fluid, and saliva. The urine also contained excessive indolylacetic and indolyllactic acid. Hypoglycemia was present even after feeding. Because of the indole components excreted in the urine, confusion

with phenylketonuria is possible. Dancis and colleagues described a further case. A year before death, the amino acids were not demonstrable in the urine but the keto acids were present in excess. Studying the keto acids in the urine of a patient, Menkes, who with Hurst and Craig first discovered this disease (in 1954), found especially α-ketocaproic acid. The clinical picture (Menkes) is that of a cerebral degeneration with its onset in the first week of life. This disease illustrates not only the progress currently being made in biochemical genetics but also that in elucidation of "primary amentia."

Mackenzie and Woolf suggested that either step B or C is defective in the following metabolic pathway of the three-branched, aromatic amino acids valine, leucine, and isoleucine:

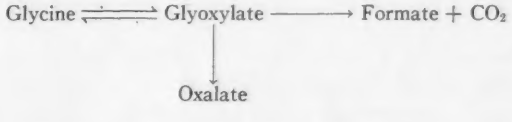


The accumulation of metabolites interferes in some way with tryptophane metabolism so that indolylacetic and indolyllactic acids are excreted in the urine as in phenylketonuria.

412. Methemoglobinemia. In one case reported by De Pree and Hickman, congenital heart disease was diagnosed until it was found that 3 siblings had also been cyanotic from birth. Three families with a total of 7 affected persons were reported.

413. Oxaluria and oxalosis (Katzuni and Sanbank). Scowen and coauthors described the pathologic changes of a case described by Archer and colleagues (1958). Scowen, Watts, and Hall described five further families with primary hyperoxaluria. In two families in which the parents were normal, the condition occurred in 2 and 5 siblings, respectively. In one family out of eight now studied by this group, the parents were first cousins. The sex incidence appears to be about equal. The inheritance is probably autosomal recessive.

The oxidative metabolism of glycine is thought to proceed in the following manner (Crawhall and co-workers):



Crawhall, Scowen, and Watts studied cases of oxaluria using C^{13}-labeled glycine and concluded that "primary hyperoxaluria arises from an inborn metabolic error involving a failure to degrade glyoxylate normally, and that an abnormal conversion of glyoxylate to oxalate is secondary to this error."

Pathologic studies of 2 cases of oxalosis were reported by Hughes. A case report was provided by Pysah and coauthors.

Winer mentioned the following two methods for identifying oxalate in urinary stones:

a. Powdered stone and 2 to 3 drops of 10 per cent HCl; if no effervescence, cool and add pinch of manganese dioxide; do not mix. Result: tiny bubbles of gas explosively released from bottom.

b. Char small fragment on spatula; add 2 drops of 10 per cent HCl. Result: foaming effervescence.

414. Pentosuria (Touster). In a long review, Schreier discussed "The Nondiabetic Melliturias" under the following headings among others:

Galactosuria
Fructosuria (levulosuria)
Pentosuria
Saccharosuria (sucrosuria)

Bozian and Touster performed loading experiments with D-glucurono-lactone (the presumptive direct precursor of the urinary L-xylulose in pentosurics) in an attempt to distinguish between a renal and an enzymatic mechanism in the disease. Normal subjects had no detectable increase in plasma xylulose, whereas pentosuric individuals showed a marked increase. The authors concluded that the results exclude a renal mechanism and that loading tests "may be of value in detecting heterozygotes. . . ." They comment that a comparison of L-xylulose-xylitol enzyme (presumably triphosphopyridine nucleotide-xylitol dehydrogenase) in normal and pentosuric liver will be the definitive way to study the nature of pentosuria.

415. Phenylketonuria (LaDu). Leonard reported an 8½-year-old girl with phenylketonuria whose IQ was 70.

Wortis and Giancotti described simple test papers for mass screening for phenylketonuria. Two such papers are available: (1) Lilly Research Laboratory test paper (RT 974) and (2) Phenistix of Ames Co., Inc. The Lilly paper was used in the trial. Phenylpyruvic acid in the urine produces a color change from the original yellow white to a blue of varying intensity. Amounts of 15 to 20 mg. per 100 c.c. are detectable. Other color changes include the following: phenol, blue; pyruvic acid, red; para-aminobenzoic acid, red; salicylic acid, purple; homogentisic acid, purple changing to brown. False positive "blue" tests were found in children who took aspirin or Thorazine. The test should be useful in screening for alkaptonuria. In general, the test will have most usefulness in the screening of newborn and other young infants and of large populations of mentally retarded children. Tests for phenylketonuria were also discussed by Gibbs and Woolf and by Rupe and Free.

Hasel and Brunsting confirmed the distinctive characteristics of blond, fair hair and blue eyes in 17 cases of phenylketonuria. The fact that the study was done in Minnesota may, however, have something to do with this result. Contrary to previous reports, ability to tan on exposure to artificial light or sunlight was not inhibited. Histochemical studies suggested that pigmentary activity of

epidermal melanocytes is not impaired. They subscribed to the view that the pigmentary defect is the result of competitive inhibition of melanin formation by phenylalanine. Dancis stated the same opinion—that phenylalanine competes with tyrosine for the enzyme tyrosinase which is necessary for the formation of DOPA.

416. Porphyria (Boackle). Dean and Barnes, in the patients with porphyria descendant from a pair of early Dutch settlers who married in Capetown in 1688, concluded that the disease (which they termed "porphyria variegata") is distinct clinically and chemically from acute, intermittent porphyria, studied in Sweden by Waldenström. They are, however, both inherited as autosomal dominant traits.

Barnes contrasted the biochemistry of porphyria occurring in South African white persons with that occurring in Sweden. In Swedish, acute, intermittent porphyria, no cutaneous manifestations occur and large amounts of δ-aminolevulinic acid and porphobilinogen are demonstrable in the urine. In porphyria variegata of the white South African (v.s.), both acute intermittent and cutaneous manifestations occur and large amounts of copro- and protoporphyrins are demonstrated in the urine. In the Bantu of South Africa, porphyria occurs commonly, manifested almost exclusively by cutaneous symptoms. There is no proof of a genetic basis; the cause may be malnutrition in early years of life. The affected Bantu demonstrate higher urinary excretion of porphyrin precursors (e.g., δ-aminolevulinic acid) than white South Africans, but lower than Swedes; they demonstrate higher excretion of copro- and protoporphyrins than the Swedes, but lower than the white South Africans.

Goldberg reviewed in detail all features of acute, intermittent porphyria on the basis of 50 cases. With the use of paper chromatography for the detection of trace amounts of porphobilinogen in the urine, he conducted a genetic survey of eleven families confirming the impression of irregular dominant inheritance. He estimated that as many as half those carrying the gene may not excrete porphobilinogen or develop symptoms. Of 18 subjects in remission, 5 did not excrete porphobilinogen. Attacks, with abdominal and neurological symptoms, were especially likely in the first trimester of pregnancy and soon after delivery. Barbiturates, especially those containing an allyl group, precipitated attacks. Hypertension was found in 28 of the 50. Tachycardia seemed a good index of activity of the disease.

Clinical and autopsy findings in 2 cases of acute intermittent porphyria, with particular reference to the nervous system, were described by Nalf, Berry, and Schlezinger. Curnow, Morgan, and Sarfety reported on family studies.

Bleifer and Alphas reported on a Negro family in which the father and a 19-year-old daughter had acute, intermittent porphyria. In all, 4 of 5 children showed porphobilinogen in the urine. A son may have had the disease, misdiagnosed as poliomyelitis, at age 6. Both symptomatic acute, intermittent porphyria and porphobilinogenuria are rare before puberty. The youngest sibling with porphyrinuria in this family was aged 6 years.

Mellinkoff and colleagues found excessive aminoaciduria in this disease. Watson and colleagues and Rimington compared human and bovine erythropoietic porphyria.

417. Pseudocholinesterase, hereditary defect in. Kalow and his colleagues have pursued interesting studies, demonstrating the following points:

a. There is not an absence of pseudocholinesterase in cases of succinylcholine sensitivity, but rather the enzyme present is atypical in its behavior with regard to a number of substrates.

b. A sensitive method for distinguishing the two types of esterase is the inhibition test using dibucaine (Nupercaine)—"normal" pseudocholinesterase is more sensitive to inhibition than is atypical pseudocholinesterase. The Dibucaine Number (DN) was proposed as a measure of esterase activity (DN = 100 [1 − Y/Chi]), where chi is esterase units without inhibitor and Y is esterase units with inhibitor. Using benzoylcholine as the substrate, dibucaine produced 77 to 83 per cent inhibition in a majority of subjects, 53 to 67 per cent inhibition in the "intermediate," and 16 to 24 per cent in persons with atypical cholinesterase.

c. The distribution of DN among members of families of persons with "low pseudocholinesterase" suggested that there are two autosomal allelic genes, each determining a different type of esterase. The homozygotes appear to have either the normal or the atypical esterase in their serum, while the heterozygotes possess a mixture of these two enzymes.

d. Kalow and Gunn estimated, on the basis of a study of 2,000 healthy Canadians, that the gene for atypical esterase has a frequency of 0.019 ± 0.002. The frequency of atypical homozygotes is about one in 2,820 (S.E. ranging from one in 2,290 to one in 3,650). The frequency of heterozygotes is 3.77 ± 0.43 per cent.

Harris and Whittaker studied the material in potato peel which is, like dibucaine, an inhibitor of pseudocholinesterase and demonstrated that, as with dibucaine, three genotypes could be distinguished. They raised the question of whether the naturally occurring inhibitor in potato could play a role in maintenance of the polymorphism in the population.

418. Wilson's disease. Enger described a case with normal serum copper and normal serum ceruloplasmin. He suggested that estrogens, increased because of the cirrhosis, had raised ceruloplasmin. (Bearn [1957] showed that administration of estrogen to patients with Wilson's disease may cause a rise of ceruloplasmin levels into the normal range.) That this is not the explanation is suggested by the 2 brothers with typical Wilson's disease reported by Sass-Kortsak. Both had normal levels of ceruloplasmin. The finding suggests rather that there may be genetic heterogeneity in the hepatolenticular syndrome and that the mechanism of this disease is still obscure. Specifically, the role of ceruloplasmin is not established. Rosenoer and Franglen likewise reported a typical case of Wilson's disease with normal serum ceruloplasmin. Bearn commented on the wide scatter of serum ceruloplasmin levels in Wilson's disease.

VOL 12 196

Barveau, Reilly and Kirsner, in the asymptomatic siblings of patients with Wilson's disease, found normal serum ceruloplasmin, but high plasma and urinary copper and increased copper in the liver. They suggested that depressed serum ceruloplasmin may be a secondary phenomenon and not the primary defect of Wilson's disease. On the other hand, using Ravin's colorimetric technique for estimation of serum copper oxidase (ceruloplasmin) activity, Lygren and his colleagues diagnosed Wilson's disease 14 months before hepatosplenomegaly was detectable and 17 months before the onset of symptoms. Aminoaciduria developed late, in that it was absent 3 months before death.

Lygren described a family in which several members had juvenile cirrhosis and others hepatolenticular degeneration. He suggested that juvenile cirrhosis may often be an incomplete form of Wilson's disease. His point, which is not new, is that Wilson's disease appearing early in life is predominantly or exclusively hepatic in its manifestations.

OL.
12
960

Sanders, Miller, and Richards described a method for the preparation of ceruloplasmin.

The copper-eliminating effects of penicillamine were confirmed by further experiences reported by Seven and associates. How the effect of penicillamine was discovered accidentally is described by Seven, Kliman, and Peterson: One of their patients with Wilson's disease developed leukopenia while receiving a chelating agent. With administration of prophylactic penicillin, increase in urinary copper excretion was maintained despite discontinuation of the chelater. Scrutiny of the chemical structure of breakdown products of penicillin suggested that penicillamine is the effective agent. Side effects of penicillamine consist mainly of gastrointestinal symptoms. Walshe referred to the occurrence of 3 cases of granulocytopenia with penicillamine and raised the question of whether the agent may provoke a deficiency of pyridoxine.

Scheinberg and Sternlieb commented that therapy effects improvement in symptoms in the central nervous system, but not in hepatic symptoms. Earlier detection and earlier institution of therapy are probably required.

Beard described schizophrenia in a patient with Wilson's disease. Despite the reports of low ceruloplasmin levels in uncomplicated schizophrenia, he was forced to conclude that the rarity of the association suggests that it was mere coincidence in his patient. He gave an extensive review of ceruloplasmin.

Taylor, Jackson, and Jensen compared splanchnic hemodynamics in 4 cases of Wilson's disease with that in 29 of Laennec's cirrhosis (all with splenomegaly). They concluded that the changes in Wilson's disease resemble much more those in extrahepatic portal venous obstruction. Since the portal vein was patent in its extrahepatic portion, as demonstrated by portal venograms, the obstruction must be located in the intrahepatic radicles of the portal vein.

Litin and colleagues found hypercalciuria in 4 of 5 patients with Wilson's disease. In one there was bilateral nephrocalcinosis and in one, renal stone. The rarefaction of bone in this disease may be explained by a renal loss of calcium.

Bihl reported a 26-year-old woman with Wilson's disease who demonstrated improvement of neurological and hepatic signs late in pregnancy and in the

puerperium. A normal-term infant was delivered. Scheinberg and Sternlieb discussed the hepatic aspects of Wilson's disease.

419. Xanthinuria. Dickinson and Smellie restudied the patient with xanthinuria reported by Dent and Philpot (1954). There were no other cases in the family and no parental consanguinity. The patient, a child presenting with xanthine urinary stones, excreted essentially no uric acid. On restudy, specific enzymatic methods were used for determination of uric acid, xanthine, and hypoxanthine. Hypoxanthine excretion was variable and low. The renal clearance of xanthine was very high, which suggests that there may be a complete failure of tubular resorption. The authors postulated a defect in xanthine oxidase in the liver and renal tubule cell.

420. Miscellaneous. In a study in Muscogee County, Georgia, Keltz and Comstock found higher serum globulin levels in 122 Negroes than in 75 white persons and concluded that it "may well be a racial characteristic." Similar results have been found in studies in Africa. Other have concluded that most or all of the difference involves the γ globulins. Keltz and Comstock found no evidence that the difference was related to syphilitic or tuberculous infection. Esterly has found the same differences in Baltimore in studies of 600 persons equally distributed among the two races and two sexes. Furthermore, by quantitative paper electrophoresis, γ globulin in Negroes has been shown to account for the excess globulin. Zak and Good determined serum γ globulin by a sensitive immunochemical method. Changes in level with age are given, but no differences between white persons and Negroes were considered.

See Bigwood and colleagues for a general discussion of aminoacidurias.

VOL. 12 196

VIII. CONGENITAL MALFORMATIONS

421. Kalter and Warkany reviewed extensively the subject of experimental teratogenesis.

422. The National Foundation (formerly the National Foundation for Infantile Paralysis) announced in 1958 a decision to broaden the scope of its program to include congenital malformations. In April, 1959, a symposium on congenital malformations was held; the papers of the participants were published in the August, 1959, issue of this journal (Warkany, Fraser, Wilson, Matson and McIntosh).

Warkany reviewed the historical development of understanding of congenital malformations.

Fraser's review of methods and results in the study of congenital malformations in man should prove especially useful. Methods were discussed according to the following outline:

The Epidemiologic Approach
- Prevalence
- Regional variation in frequency
- Seasonal variation

Social class
Parental age
Parity
Correlation with epidemics
Correlation with other environmental extremes

The Genetic Approach
Pedigree analysis
The contingency method (This method measures the frequency of involvement in relatives of probands. It is useful also in establishing etiological associations. For example, the fact that spina bifida aperta occurs with increased frequency in siblings of probands with anencephaly suggests an etiological relationship even though they do not occur always in the same individual.)
The twin method
The consanguinity method
Racial comparisons
Cytologic studies

The Embryologic Approach
Pregnancy studies
Retrospective studies
Prospective studies. (Although prospective studies are theoretically preferable, the main disadvantages are the enormous number of cases which must be studied to get meaningful results and the uncertainty about what questions to ask to get positive results. "At present it must be admitted that no teratogenic factors have been identified by prospective studies.")

Experimental teratogenesis was reviewed by Wilson. Matson reviewed the surgical treatment of birth defects involving the central nervous system. He estimated that about 40 per cent of admissions to the neurosurgical service of the Children's Medical Center, Boston, fall in this category.

McIntosh emphasized the difficulties in definition of congenital malformations (are inborn errors of metabolism to be included?) and discussed prospects in elucidation of pathogenesis and in treatment. He emphasized the importance of the patient's attitude toward his disease. "The man I think of most often in this context is President Eliot of Harvard, who went through life with one half of his face marred by an undisguised, inescapable portwine stain. Not the least admirable aspect of his moral victory over his disability is the fact that his great contribution lay in the field of education. And not the least challenging of the considerations which arise when one is confronted with an infant or child with a congenital deformity is the thought that his full potential may bear little direct relation to the malformation present."

423. Hummel of the Jackson Laboratory described the effects of an interesting new mutation in mice which she refers to as the "disorganization gene." It is lethal in the homozygous state and incompletely penetrant (72 per cent)

in the heterozygous state. A very instructive feature is that which gives the gene its name; it disrupts orderly organogenesis and induces a great variety of anomalies in structures derived from all germ layers. The lack of patterning of the multiple defects is a distinctive feature. In a sample of 500 fetuses, anomalies included cranioschisis and exencephaly in 53 per cent, hamartomas (misplaced supernumerary organoids and tissues) in 40 per cent, anomalies of appendages (polydactyly, accessory long bones, abnormal osseous fusions, etc.) in 33 per cent, defects of the eye in 21 per cent, pharyngeal defects in 18 per cent, gastroschisis in 16 per cent, and so on.

424. Schull, after an analysis of data from Japan, concluded that congenital malformations are increased in consanguineous matings, suggesting a genetic factor in their etiology.

VOL. 12 1960

425. Warkany and his colleagues described a malformed infant born of a woman who had attempted abortion by taking 12 mg. of 4-aminopteroylglutamic acid (Aminopterin) during the tenth week of pregnancy. The infant showed intrauterine growth retardation, cranial dysostosis, cleft palate, mandibular hypoplasia, and auricular anomalies.

In Dublin, Coffey and Jessop, in a prospective study during the pandemic of Asian influenza in October and November, 1957, noted congenital malformations 2.4 times more frequently in the offspring of women who had influenza during pregnancy than in those who did not. The abnormalities were mainly of the central nervous system and the commonest was anencephaly. The risk of malformation was much greater when influenza occurred in the first trimester of pregnancy.

426. Odfield has operated on 1,041 children with harelip and/or cleft palate. The sex incidence in his series is given in Table V.

TABLE V

	BOYS		GIRLS		
	NUMBER	PER CENT	NUMBER	PER CENT	TOTAL
Harelip	94	40	139	60	233
Harelip–cleft palate	137	30	313	70	450
Cleft palate	214	60	144	40	358
Totals	445		596		1,041

427. Raybuck and Mantei did a detailed anatomic study of the feet of a 60-year-old Negro with bilateral *clubfoot* (talipes equinovarus). No treatment had been employed. The muscles, tendons, and ligaments were found to have entirely normal anatomic attachments despite severe derangement of bone structure. Robins described clubfoot in the house mouse behaving as an autosomal recessive trait. Affected males predominated somewhat over affected females (3 males to 2 females).

428. Because of the predominance of phenotypic females among *anencephalic* fetuses, Bearn was prompted to determine nuclear chromatin in 24 anencephalic

individuals, 21 female and 3 male, by external genitalia. In all, the chromatin study revealed findings consistent with the phenotype. Harnden, Briggs, and Stewart likewise found a chromosome count of 46 in 4 cases of anencephaly and found that the sex chromosome constitution agreed with the phenotypic sex. Therefore, the excess of females cannot be accounted for on the basis of a chromosomal aberration. Of course, the possibility of a lesser chromosomal aberration, such as a small translocation not detectable by present techniques, has not been excluded as the cause of anencephaly. As evidence of nongenetic factors, the authors cite the case of Litt and Strauss (1935) in which only one of presumably monozygotic twins was anencephalic. (Thompson reported anencephaly in one of twins, but unfortunately no information on zygosity was obtained.) Further, Polani mentioned study of 16 anencephalic individuals at or near term; in all, the sexual phenotype and nuclear sex and internal organs were in agreement. He suggested that the female preponderance at term might be explicable on the basis of a selective loss of male anencephalic embryos early in pregnancy. He studied 6 anencephalic embryos lost in the first weeks of pregnancy and found all to be "chromatin negative." In 4, the gonad was sufficiently developed to be identified as a testis.

Searle reviewed the evidence suggesting a complicated intertwining of genetic and environmental factors in anencephaly and presented data on the occurrence of anencephaly in Singapore.

429. Fawcitt reviewed the subject of congenital anomalies of the spine with particular reference to the radiologic aspects in early life and to coronal cleft vertebrae and spina bifida. The cervical spine tends to show errors of segmentation with fusion of vertebrae, as in the relatively common Klippel-Feil deformity. Hemivertebrae are usually seen in the dorsal spine. The lumbar spine and upper sacrum are most commonly affected by spina bifida in varying degrees of severity. Abnormalities of the sacrum are usually hypoplasia or aplasia, generally associated with malformation of the urinary tract. A control vertebral cleft seen on lateral view of the spine is sometimes seen in the fetus in utero. It usually disappears later. A bifid lesion of the first sacral vertebra is extremely common. With growth it disappears. Fawcitt found in 500 children, excluding cases of gross spinal anomaly, frequencies of 94 per cent among those 5 years of age or less and 75 per cent in the group 11 to 16 years of age.

430. Ivemark, Oldfelt, and Zetterström described what may be a previously unrecognized hereditary disease—*familial dysplasia of the kidneys, liver, and pancreas.* Among the offspring of unrelated parents, the second and third children died at 11 weeks and 20 days, respectively. Histologically, the kidneys showed primitive tubules and vascular abnormalities. The liver and pancreas were said to contain "embryonal connective tissue." The organ distribution and some of the histologic characteristics suggest fetal polycystic disease.

Searle found *absence of the spleen* to be one expression of the Dh gene ("dominant hemimelia") in the mouse. Both heterozygotes and homozygotes entirely lack the spleen. Mice homozygous for the gene also have severe malformation

of the extremities and of the urogenital and alimentary tracts, so that the homozygous state is lethal.

Frank and Piper described *congenital pulmonary cystic lymphangiectasis* (or lymphangiomatosis) in 2 infants; one was stillborn and the other lived only about 2 hours. In one case there were also cystic lymphangiectases in the heart, pancreas, kidneys, and mesentery. Apparently these cases are fatal early and would not be confused with other types of cystic lung disease.

431. Stevenson and Warnock studied the outcome of all pregancies terminated in women resident in Belfast in 1957. Among 9,526 pregancies identified, there were 8,300 live births, 219 stillbirths (2.3 per cent), and 1,127 abortions (11.8 per cent) between the fourth and twenty-seventh weeks of pregnancy. Of the 8,519 live births and stillbirths, gross malformations were found in 120; of the pregnancies related to these cases, hydramnios was a complication in at least 33. The high incidence of anencephaly in Belfast was again noted—4.58 per 1,000 livebirths and stillbirths. Stevenson, Dudgeon, and McClure estimated that the true abortion rate in Belfast in 1957 lay between 11.8 and 16 per cent, with not more than one per cent being criminally induced. Stevenson attempted nuclear sex determination on the aborted concepti by studying chorionic villi. Although the technical difficulties made conclusions difficult, there seemed to be in the 345 abortions in which a sex could be assigned a preponderance of males. Furthermore, the male preponderance seemed larger than that in live births and stillbirths in the same population.

VOL. 12 1960

IX. ALIMENTARY TRACT, INCLUDING PANCREAS, BILIARY TRACT, AND LIVER

432. McNab Jones described pharyngeal pouch in 5 members of two generations, with a sixth possible case. The pouch developed between the ages of 60 and 70 years. Dysphagia with a sensation of food sticking in the throat was the main symptom. Hird and Hortenstine found multiple epiphrenal diverticula in a 72-year-old man and 2 of his children, aged 38 and 43, with a tracheoesophageal fistula at birth in a grandchild, the child of an asymptomatic but not thoroughly studied daughter of the man. The diverticula were located in the lower half of the esophagus.

Stomach and duodenum: 433. Almond described 5 siblings with peptic ulcer (4 of 6 sons, one of 6 daughters). All 5 had partial gastrectomy! All were blood group A; none smoked heavily; none seemed to be the "ulcer type."

The matter of ABO blood groups and of secretor status in persons with peptic ulcer and in their relatives was further discussed by Clarke and by McConnell. Comparing the secretor status in controls (851) with that in patients with duodenal ulcer (1,104) and gastric ulcer (138), they found a significant difference with respect to ABH nonsecretion (36.6 per cent in duodenal and 27.5 per cent in gastric ulcer; controls, 24.3 per cent). Using fucose content of the saliva as an index of total amount of blood group substance in the saliva, they concluded that there is no difference between patients with duodenal ulcer and controls (Clarke and colleagues). Most nonsecretors of ABH are presumed to secrete Lewis substance only.

Sievers found gastric acid and pepsinogen secretion to be greater in group O individuals and less in group A individuals—findings consistent with the blood group associations with peptic ulcer, gastric cancer, and pernicious anemia. Jackson emphasized the association of peptic ulcer with hereditary hyperparathyroidism and suggested that the parathyroid disease merely "brings out" a genetic tendency to peptic ulcer which is frequent in the population.

Pender described a man with the Zollinger-Ellison syndrome: he had gastric hypersecretion, recurrent peptic ulcer, and islet cell adenoma of the pancreas. A daughter had earlier undergone an operation for removal of benign adenoma of the pancreas.

434. Mack presented 2 cases of hypertrophic pyloric stenosis in adults. Both, men, had been subjected to surgical operation because of a suspicion of gastric malignancy. This may be the same disease as the disease in infants, in which a genetic factor is possible but unclear (McKeown and MacMahon, 1955).

L.
2
60

Small intestine: 435. Cases of the Peutz-Jeghers syndrome (intestinal polyposis and melanin pigmentation of the buccal mucosa, lips, and digits) were described by Falkinburg, by Guillard and colleagues, and by Megevand. Photographs of the oral lesions of 20 reported patients were reproduced by Zegarelli and coauthors. Kutscher and colleagues published a follow-up on cases previously reported by others. The similarities from patient to patient are more impressive than any differences. Katzen and coauthors described a parent and 2 children with this syndrome. They subscribed to the view of Dormandy and of Bartholomew that the small intestinal tumors are not premalignant. Without supporting data they suggest that the polyps of the large bowel may undergo malignant change. Rintala analyzed the histologic state of polyps removed from a father and his 2 daughters in eight operations. The nature of the polyps of the small intestine as hamartomata and therefore not premalignant was confirmed. The polyps of the colon, however, had more the appearance of adenomata, in that they were composed essentially of only goblet cells. He stated that true malignant degeneration had been reported in only 2 cases and in no case have metastases been found.

436. Lechner and Connolly list the Peutz-Jeghers syndrome, neurofibromatosis (von Recklinghausen's disease), and Osler-Rendu-Weber disease among the conditions which may be associated with benign bleeding tumors of the jejunum. Farrar and Chappell found neurofibromatosis to be the cause of severe gastrointestinal bleeding in a 50-year-old man. (See also Darling and Welch.)

437. Gross and his colleagues reported 60- and 63-year-old brothers with *Whipple's disease.* Puite and Teshek (1953) reported the only other familial case. Diabetes and psychiatric disorders seem especially frequent. No case of Whipple's disease has been reported in a Negro. It is now known that the

designation "intestinal lipodystrophy" is a misnomer; the inclusion materal is a glycoprotein. Experience with this disease, as with Hurler's syndrome ("lipochondrodystrophy" is a misnomer), indicates that eponyms are sometimes preferable.

438. Weijers and van de Kamer performed a gliadin tolerance test in patients with *celiac disease.* A rise of blood "glutamine" level of more than 40 per cent above the fasting level after an oral dose of 350 mg. per kilogram of gliadin was considered abnormal. An abnormal test persists into adulthood. It appears that what is determined as glutamine in the blood is not free glutamine but rather glutamine contained in peptides. The presence of defective proteolytic enzymes in the bowel is postulated as the basic abnormality in celiac disease.

Sheldon, of the Great Ormond Street Hospital, London, in a review of celiac disease mentioned familial aggregation. Assuming that celiac disease in patients with a striking improvement on a gluten-free diet has a common etiology, Carter, from the same hospital, studied genetic features in 88 such patients. The risk in the general population was placed at about one in 3,000; in contrast, 5 of 205 brothers and sisters, 2 of 85 fathers, one of 580 aunts and uncles, and one of 806 cousins had proved celiac disease or idiopathic steatorrhea. No relation to maternal age, birth order, social class, other gastrointestinal disorders, allergy, or diabetes mellitus was demonstrated. (Ebbs [1950] had suggested both familial aggregation and a relationship, within families, between celiac disease and diabetes. At the Massachusetts General Hospital, Joske and Benson [1958] found that 71.4 per cent of patients [N = 28] with adult, nontropical sprue, which is probably the same disease as celiac disease of childhood, were of blood type O, as compared to the value of only about 45 per cent for the general white population of the United States.) Carter suggested that the genetic factor is only a predisposing one.

Large intestine: 439. Gardner's syndrome (multiple polyposis of the colon with osteomata and soft tissue tumors such as desmoid and epidermoid cysts) was discussed by Smith and by Collins.

Cole and Holden confirmed the interesting observation that after colectomy and ileoproctostomy for familial polyposis, rectal polyps undergo spontaneous regression. (McLachlin made similar observations in familial cases.) Their colleague at Western Reserve, Leuchtenberger, demonstrated Feulgen-positive granules in the cytoplasm of rectal and colonic polyps (Lab. Invest. 3:132, 1954). Leuchtenberger suggested that the regressing rectal polyps showed a progressive decrease in the content of Feulgen-positive cytoplasmic inclusions. Cole raised the question of whether the ileal fluid may be unfavorable to polyps—few polyps occur in the cecum and the density of polyps in the colon may show a gradient from cecum to sigmoid; polyps are rare in the small intestine (except in the Peutz-Jeghers syndrome in which the polyps are hamartomas not adenomas, ¶435); after ileoproctostomy the polyps nearest the anastomosis disappear first. Although the polyps undergo regression, carcinoma may still occur in the rectal stump.

440. Swenson, who has had a large experience with *Hirschsprung's disease* (aganglionic megacolon), feels the disease is definitely hereditary. In one sibship there were 3 proved cases and 2 probable cases. One set of identical twins had the disease. A mother with Hirschsprung's disease had one affected child out of 4. Swenson estimated, however, that only about 2 per cent of cases have recognized disease in other members of the family. Males predominate by about 4 to 1. The aganglionic state involves the distal colon which is contracted, producing partial obstruction; the more proximal colon becomes hypertrophied and greatly dilated. About 40 per cent of cases also have megalobladder and a small proportion of these have megaloureter as well.

Swenson, Fisher, and Gherardi showed that rectal biopsy is a safe and effective way to diagnose Hirschsprung's disease in infants and children with atypical manifestations. Deficiency of Auerbach's and Meissner's plexuses is diagnostic.

Pancreas: 441. Peterson did sweat electrolyte tests on 262 adults. A "positive" test like that in cystic fibrosis was noted in 14: 10 had chronic severe endobronchial disease, 2 had peptic ulcer, one had chronic pancreatitis, and one had allergic bronchial asthma. He suggested that cystic fibrosis is not exclusively a disease of children. This was not a genetic study. Study of parents of patients with cystic fibrosis for evidence of pancreatic, hepatic, pulmonary, and other dysfunction would be very interesting and possibly easier to interpret as far as relation to the "cystic fibrosis gene" is concerned.

Smoller and Hsia studied the families of 38 patients with cystic fibrosis. About one-half of parents and about one-third of siblings had a sweat sodium measurement above the limit of normal. Koch studied mucoviscidosis in adults and concluded that the disorder is expressed in heterozygotes, i.e., is a dominant trait. However, the finding of elevated sweat electrolyte levels in *one* parent may be explicable by the relative nonspecificity of the expression. Because of the wide overlap of heterozygotes and normal individuals with respect to sweat electrolytes, it is by chance to be expected that frequently only one parent will show definitely elevated values. This interpretation is applicable also to the findings of Uchida and colleagues (¶322). Koch emphasized also a high frequency of peptic ulcer in members of "cystic fibrosis families." The ulcers were unusual in being predominantly gastric.

Koch and Lapp described the clinical and pathologic finding in 3 men who died at the ages of 44, 51, and 66 years, respectively. All 3 had (1) chronic pulmonary disease with bronchiectasis, emphysema, and cor pulmonale, (2) excretory pancreatic insufficiency, and (3) excessive loss of sodium and chloride in the sweat. Autopsy revealed viscid mucous plugs in the bronchioles and mucous glands of the gastrointestinal tract and fibrous changes in the pancreas.

Dunnill found at autopsy, in a 17-year-old patient with cystic fibrosis, extensive squamous metaplasia of the pleura.

Brogan described methods for studying carbohydrate complexes in bronchial secretions. The methods might be useful in the investigation of persons homozygous or heterozygous for the gene for cystic fibrosis of the pancreas.

As a simplified screening test for cystic fibrosis of the pancreas, Knights, Brush, and Schroeder suggested silver-chromate–impregnated filter paper. It is cheaper to prepare than the agar plates, is easier to store, and can be used as a permanent record. A simple, quick screening test for sweat chloride was also outlined by Gluck.

Holman, Blanc, and Andersen found a conspicuous decrease in aortic atherosclerosis in cystic fibrosis cases, a finding which like the deficiencies of fat-soluble vitamins is to be expected from the defect in fat absorption.

Hsia studied birth weight in relation to gestation time, maternal age, parity, and survival in 123 children with cystic fibrosis and 144 unaffected siblings. The data were compared with those of Karn and Penrose (1951) for normal infants. Birth weight was significantly lower in affected children than in their unaffected siblings. The effect was greatest in those children who had died by the time of the study and in those children who displayed predominantly "duodenal" symptoms than in those with predominantly pulmonary symptoms. Among unaffected siblings the mean birth weight in those with sweat sodium levels of 50 mEq. per liter or more was lower than in the others.

Roberts suggested that the fundamental defect in fibrocystic disease of the pancreas may reside in the chemical mediator of the nerves to the various glandular structures involved. "If the specific choline esterase were diminished in amount, or alternatively the acetylcholine were more resistant than usual to the action of acetylcholine esterase, then the acetylcholine released would act abnormally long and so would cause oversecretion by the glands. Alternatively, the amount of acetylcholine released at the nerve-endings might be excessive." He favored the former alternative. How known features of the disease and knowledge about nervous control of gland function agree with the theory was reviewed.

442. Bartholomew reviewed *hereditary pancreatitis*, which was first described by Comfort and Steinberg (1952) and which appears to be inherited as a dominant trait. It affects females somewhat more commonly than males and has its onset early in life, even childhood. Calcification is less diffuse than in the nonhereditary form and tends to be in the form of calculi in the larger pancreatic ducts. A finding of great interest is the abnormality of amino acids in the serum and urine of patients and of some relatives who have not yet developed clinical manifestations. Excessive lysinuria is particularly distinctive.

443. Liver and biliary tract. According to Geraci, at least 26 animal species including herbivores, marsupials, and rodents have no gall bladder. Absent gall bladder is frequent in the human species also. It is absent more often in women, but the greater frequency of biliary disease in women may more often call attention to the absence of the gall bladder, when x-ray or surgical exploration is performed. Carnevali and Kunath stated that the necropsy incidence is the same in the two sexes. Kobacker (1950) found no gall bladder at operation on 2 sisters and none was visible by x-ray in 3 of 5 other siblings and 2 descendants of the 2 patients.

(See ¶397 for a discussion of the hereditary bilirubinemias.)

VOL. 12 1960

Kjølbye and Nielsen found an increased frequency of blood group A in patients with cholelithiasis. The largest excess of group A was in females under the age of 50.

In 100 consecutive patients in whom a gall bladder operation was performed at his hospital, Jackson found that one parent in 33 had had definite gall bladder disease. The possibility of sex-linked dominant inheritance was suggested but seems unjustified by the data.

X. BLOOD AND HEMATOPOIETIC SYSTEM

Disturbances of the Clotting Mechanism.—

444. Quick gave a useful review of hereditary hemorrhagic diseases, dividing them into three groups: (1) hemostatic defects, (2) combined hemostatic and vascular defects, and (3) vascular defects. Koller, Vogel-Meng, and Steiner continued the annotated bibliography of the physiology and pathology of blood coagulation instituted a few years ago.

445. A symposium on "Blood Clotting Factors" held at the Fourth International Congress of Biochemistry in Vienna in September, 1958, was published in 1959 under the editorship of Deutsch.

Brinkhous (Chapel Hill) and De Nicola (Pavia) edited the proceedings of an international symposium held in Rome in 1958 on hemophilia and other hemorrhagic states. Some aspects of the symposium are reviewed here:

Brinkhous reviewed the evidence that Johann Lukas Schönlein (1793-1864), professor of special pathology and therapy, Würzberg, introduced the term "hemophilia" in his lectures in the 1820's. It is possible that the original term was "haemorrhaphilia," rather than the senseless "hemophilia."

Two female patients with hemophilia A were described by Pavlovsky and de Pavlovsky (Buenos Aires). Both were daughters of a hemophilic man and a normal woman who came from a family with no record of a hemophilic case. Lenggenhager and Büchler (Bern) described two simple tests for distinguishing hemophilia A and B.

Previous to von Willebrand's report (1926) of a new bleeding disease in the inhabitants of the Islands of Åland, located in the Baltic Sea between Sweden and Finland, only three bleeding states were known—hemophilia, thrombocytopenic purpura, and Osler-Rendu-Weber hereditary hemorrhagic telangiectasia (Quick, Milwaukee). Von Willebrand thought the disease he described was a "thrombopathy" or "thrombasthenia," that the prolonged bleeding time was the result of a qualitative defect of platelets (¶450). The prothrombin consumption test and the thromboplastinogen activity test help differentiate between a platelet defect and a plasma defect as the basis of hemorrhagic disorders characterized by a prolonged bleeding time. Pseudohemophilia A is due to a plasma defect, inherited as an autosomal dominant trait. It is characterized by purpuric bleeding. In one of the families on Åland, both parents were bleeders and of their children 5 were severe bleeders (homozygous ?), 2 were mild bleeders (heterozygous ?), and 5 were normal. Pseudohemophilia B (Synonyms: vascular

hemophilia, angiohemophilia), manifested not only by purpuric bleeding but also by deep bleeding like that of hemophilia, is inherited as an autosomal recessive trait. By laboratory tests, subclinical abnormalities of clotting can be demonstrated in heterozygotes. Although the Åland cases were probably not of this type, there are indeed cases in which bleeding with prolonged bleeding time is due to defective platelet function as revealed by the prothrombin consumption test and by correction of the defect by normal platelets. The defect behaves as an autosomal dominant characteristic. Several other contributors emphasized the difficulties in sorting out the several varieties of hemophilia-like states with prolonged bleeding time.

446. Wright reported on the nomenclature of blood clotting factors and the acceptance by an international committee of four new ones. The previously well-recognized ones are the following:

Factor I. Fibrinogen
Factor II. Prothrombin. Borchgrevink and coauthors described familial hypoprothrombinemia.
Factor III. Thromboplastin (tissue)
Factor IV. Calcium

Four additional factors have now been recognized and assigned a number.

Factor V. Proaccelerin (synonyms: labile factor, plasma Ac-globulin, thrombogen, proprothrombinase, etc., etc.). A genetic deficiency causes parahemophilia.

("Factor VI" has not been assigned as a designation. A factor tentatively so designated failed to stand the test of time and closer investigation.)

Factor VII. Proconvertin (synonyms: SPCA, serum prothrombin conversion accelerator, κ factor, prothrombinogen, etc., etc.). A hereditary defect, behaving as an autosomal recessive trait, is known (Caen and coauthors; Dische and Benfield; Miller.)

Factor VIII. Antihemophilic globulin (synonyms: antihemophilic globulin A, AHF, plasma thromboplastic factor, etc., etc.). A genetic defect results in classic hemophilia, a sex-linked recessive trait.

Factor IX. PTC, plasma thromboplastic component (synonyms: Christmas factor, antihemophilic globulin B, etc., etc.). A genetic deficiency results in hemophilia B or Christmas disease, transmitted as a sex-linked recessive trait.

By matching the above list against the list of nine hereditary defects given in ¶135, it will be evident that three factors are missing: (1) plasma thromboplastin antecedent (PTA) of which a deficiency is the basis of hemophilia C, (2) Hageman factor, and (3) Stuart-Prower factor. These, like most of the others of the list above, have been identified by the discovery of hereditary defects. Although probably inherited as an autosomal recessive trait, deficiency

VOL. 12 1960

of the Hageman factor results in no symptoms. Wright states that Stuart factor may be designated factor X.

447. Lewis and Merchant have applied the method of continuous flow electrophoresis to the study of the proteins of blood concerned in coagulation. They reported studies on hemophilia A and B.

Didisheim proposed a new method for diagnosis of classic hemophilia. At present the diagnosis rests either on (1) modifications of the thromboplastin generation test or (2) tests dependent on the use of plasma from a patient with classic hemophilia as a reagent. The first group is time consuming. Appropriate plasma may not be readily available for the second group. Didisheim's test depends on the recalification time of plasma from blood collected into Na_2 EDTA (disodium ethylenediamine tetra-acetic acid).

Horwitz, Bassen, and Simon described pseudotumor of the ilium in a patient with classic hemophilia and Silber and Christensen described it in hemohilia B. Such pseudotumors are caused by single or multiple hemorrhages resulting in destruction, expansion, and cyst formation. A malignant osteoclastic bone tumor is suggested by the x-ray appearance. Trauma is often involved in the original hemorrhage.

Pitney and Arnold quantitated antihemophilic globulin (AHF) in normal males and females, hemophilic males, and carrier females. Carrier females tend to have concentrations intermediate between normal females and hemophilic males. It was of note that normal males and females had identical levels; there seems to be no "dosage effect" dependent upon the presence of one or two genes. The authors suggested that synthesis of AHF is primarily under control of an autosomal locus. The X-borne hemophilia gene may interfere with the expression of the autosomal genes or may suppress or destroy AHF. Pitney and Arnold could not demonstrate that carriers were more readily identified by low AHF in families with mild hemophilia, a finding of earlier workers.

(See ¶385 for one mechanism of hemophilia A in a "female.")

448. Roos and Huizinga reported on a family with a coagulation deficiency, apparently of the Stuart type. The Stuart factor was so named by Graham and colleagues (1957) from the surname of the first patient with a defect of same. The defect in the Dutch family studied by Roos and Huizinga seemed to be inherited as an autosomal recessive characteristic, as in the North Carolina family of Graham and colleagues. By determination of the concentration of Stuart factor in the normal relatives of bleeders, it was possible to separate homozygotes from heterozygotes with almost complete success. Chevallier and coauthors also described cases.

449. Hemophilia B was discussed by Quick and Hussey.

450. Spurling and Sacks described studies of 2 cases with an inherited hemorrhagic disorder characterized by both a deficiency of antihemophilic globulin and a prolonged bleeding time ("vascular hemopilia"). The disorder is probably determined by an autosomal gene. It was discussed also by Jorpes.

Nilsson, Blombäck, and Blombäck described their studies of this disorder to which they chose to apply the eponym von Willebrand. They defined it as an inherited autosomal dominant hemorrhagic diathesis with antihemophilic globulin deficiency and prolonged bleeding time. Platelet count and function were normal; therefore, von Willebrand's designation of "constitutional thrombasthenia" is not warranted. In fact, some of von Willebrand's patients were restudied and normal platelets were demonstrated. Studies further showed that administration of human plasma fraction I-O of Blombäck and Blombäck controlled bleeding, corrected the prolonged bleeding time, and raised AHG level. Furthermore, the same fraction from plasma of patients with hemophilia A was similarly effective.

451. Nour-Eldin and Wilkinson described another sex-linked recessive disorder with a combined clotting defect—a deficiency of both factor VII and Christmas factor (IX).

VOL. 12 1960

452. Hermansky and Pudlah reported on 2 unrelated albinos who had hemorrhagic diathesis and peculiar pigmented reticular cells in the bone marrow. The only consistent laboratory finding was a prolonged bleeding time. The disorder may be a syndrome and may indicate genetic heterogeneity in the general category of albinos: heterogeneity has already been demonstrated by description of albinos with the Chediak-Steinbrinck anomaly of the leukocytes (¶137).

453. Welter described a hitherto unknown disorder of blood clotting which occurred in several generations of one family, transmitted probably as a simple Mendelian autosomal dominant trait. The characteristics were hepatosplenomegaly, hypergammaglobulinemia, and a hemorrhagic diathesis.

McCain, Chernoff, and Graham studied the inheritance of the Hageman trait in four unrelated families, two of which showed consanguinity. Both males and females and both Negroes and Caucasians were affected. The inheritance seemed to be autosomal recessive. (In the three informative sibships there were 3 out of 9 affected in one, 2 out of 9 in a second, and one out of 2 in the third. By the Lenz-Hogben method, 6.0084 are expected to be affected as compared with the 6 observed.) In only very few of presumed heterozygotes could a mild defect be identified. All four kindreds were ascertained through the practice of hospitals routinely to perform whole blood clotting times before operation. All "affected" persons had *no* history of unusual hemorrhage. The physiologic and pathologic implications of the Hageman factor are totally unknown. It is known that contact between glass and the Hageman factor initiates a series of reactions ending in clotting of the blood, release of a pain-producing and smooth muscle–activating polypeptide, and activation of a permeability factor (Margolis). Margolis speculated that inhaled silica dust might act differently in persons with the defect and that the factor might be a remnant of a phenomenon of biologic importance in the past. Study of the comparative physiology of the Hageman factor might contribute to the latter questions.

Platelets: 454. Shaw and Oliver described brother and sister with thrombocytopenia and congenital absence of both radii. The male died at age 8 months, of cerebral hemorrhage. Thrombocytopenia with skeletal deformities was also described in siblings by Gross and co-workers (1956). The authors suggested that the disorder in their siblings was allied to the Fanconi syndrome, in which anemia is associated with congenital skeletal and other malformations (¶465).

455. Van Loghem and colleagues demonstrated a new platelet agglutinogen in the serum of a patient (suffering from severe thrombocytopenia) after he had received several blood transfusions. They called it "anti-Zw." The anti-Zw serum agglutinated the platelet suspensions from 280 out of 287 unrelated subjects (97.6 per cent). Analysis in the families of 3 Zw-negative persons suggested simple dominant inheritance of the antigen Zw. Two categories of platelet antigens have been discovered: (1) antigens with the same specificity as red cell antigens (A, B, and Tj^a have been reported) and (2) antigens independent of known blood group systems.

L.
2
60

456. Krivit and Good described 7 males with *the Aldrich syndrome:* thrombocytopenia resulting in rectal bleeding and petechiae, eczema, and infections (purulent otitis, pneumonia, and abscesses). Most had onset with melena in the neonatal period and all died before the age of 3 years. The disorder is inherited as a sex-linked recessive trait. Histopathologic studies reveal multiple thrombi of small arterioles. Brubaker and Hammond described 3 additional cases. Splenectomy corrected the thrombocytopenia and resulted in general clinical improvement. Mills and Winkelmann, who, like Aldrich and his colleagues and Good and his colleagues, work in Minnesota, described four affected families. Special attention was given to the skin manifestations. The association of purpura with infantile eczema in a male child should bring the condition to mind. The disease has been reported in areas other than Minnesota (e.g., Huntley and Dees, 1957) and in the Negro (Wolff and Bertucio, 1957).

457. Gilon and associates described a 13-year-old girl with multiple hemangiomata and thrombocytopenia. Although perhaps the association was coincidental, the possibility of a genetic basis and of (pseudo)pleiotropy is responsible for mention here.

Qualitative defects of the platelets ("thrombasthenia") as a basis of hemorrhagic diathesis are not universally accepted as existing (¶450). Sokal, Verstraete, and Vermylen reported that 2 out of 7 members of one family showed a clotting defect apparently on the basis of such a defect.

Genetic Disorders of the White Blood Cells.—

458. Leukoagglutinins (¶324) were studied using a panel of sera of patients who had received multiple transfusions (Lalezari and Spaet). The leukocytes of identical twins showed identical reaction patterns; those of dizygotic twins did not. No 2 unrelated persons had identical reaction patterns. Family studies

were inconclusive as far as identification of specific leukocyte antigens are concerned. There was no relation between leukocyte antigens and erythrocyte antigens.

459. Rosse and Gurney described 13 cases of the Pelger-Huët anomaly in three families. One of these families represented the second reported instance in Negroes. Survival of transfused leukocytes was studied with the use of the anomalous cells as a tagging device. Most of the Pelger cells disappeared in 6 to 8 hours and none were present after 49.5 hours. They suggested that these values may be normal. Except for the morphologic difference, no definite abnormality of the Pelger leukocyte has been found. A form of pseudo–Pelger anomaly occurs in cases of leukemia. It was interpreted by Don and Moloney as an indication of derangement in chromatin formation.

Seman added a fourth genetic morphologic anomaly of the leukocyte nucleus. (The other three are the Pelger-Huët hyposegmentation, the hypersegmentation of Undritz [1943], and the Chediak anomaly.) As in the first two of the previously described anomalies, the new anomaly has no apparent pathologic implications. The anomaly consists of many tiny lobulations on the normally lobulated nucleus. Essentially, the lobulations are minute pedunculated excrescences. The family studies were not complete at the time of report.

460. Hedenberg described a case of infantile agranulocytosis probably identical to that described by Kostmann (1956). He considered the disease to be "a congenital defect of the patient's ability to utilize the sulfur-containing amino acids." Cysteine therapy had no effect, but the addition of sulfur-containing amino acids to tissue cultures of marrow cells permitted maturation of the white cells.

461. DeVaal and Seynhaeve described a "new" disease, reticular dysgenesia with congenital aleukia, in male twins, "almost certainly monozygotic," who died at 5 and 8 days of life. No leukocytes were ever seen in the peripheral blood and no myeloid elements were found in the bone marrow, although erythropoiesis and megakaryocytes were normal. There were no leukocyte antibodies in the twins or the mother.

462. Levine described hyperplastic gingivitis in a 14½-year-old boy with chronic familial neutropenia. The father and one sister and brother were said also to have "the condition." Clubbing of the fingers and hyperglobulinemia were mentioned as features. Presumably the monocytosis (25 per cent) and eosinophilia (12 per cent) were relative.

463. Leukemia (see ¶387). Hitzig and Rampini reported on leukemia in 4 pairs of twins of like sex—3 monozygotic, one dizygotic. Both were affected in one monozygotic pair. The other 3 sets of twins had only one leukemic member. The authors concluded that concordance in monozygotic twins is probably more than can be explained by chance and that a hereditary predisposition is indicated. Alternatively, radiation effect might be expected to result in increased concordance in monozygotic twins.

VOL. 12 196

Court Brown and Doll analyzed trends in adult leukemia mortality using age-specific mortality rates. The results indicate a real increase, mainly in the incidence of acute leukemia. The latter fact is compatible with the concept that increased exposure to ionizing radiation plays some part in the leukemia increase.

Murray, Heckel, and Hempelmann, in a follow-up study of over 6,400 children who had received irradiation, found a higher incidence of subsequent leukemia than in the nonirradiated group. X-ray therapy had been given for enlarged thymus, pertussis, lymphoid hyperplasia, and other conditions.

Brescia, Santora, and Sarnatora described "congenital" stem cell leukemia, fatal in a 28-day-old boy. The mother had been exposed to heavy radiation 5 months *before* conception.

The possibility of somatic mutation in acute leukemia has been suggested by the discovery of chimerism for ABO blood group (Salmon, André, and Dreyfus; Gold and associates). At least three examples have been observed. All cases have had a mixture of group A blood with group O or with "weak group A." Salmon suggested that the direction of the observed change is probably significant; in an individual of blood group O or B a clone mutant to A or in an individual of blood group O or B a clone mutant to B would have no chance of proliferating because of the presence of natural anti-A and anti-B antibodies.

Genetic Disorders of the Erythron.—

464. Druey reported a case called in French "acanthocytose," called in English (by Singer) "acanthrocytosis" (¶204). The French designation seems etymologically more correct. He suggested that the abnormality may concern the erythrocyte membrane. Parental consanguinity has been a feature of all reported cases. Three previously reported cases were known to the author. In all a neurological disorder was present—Friedreich's ataxia in one and progressive ataxia in a second. Druey's case showed cerebellar ataxia. Is it the lipoid moiety which is defective in the erythrocyte membrane and in the central nervous system?

465. Garriga and Crosby emphasized the occurrence of leukemia in the families of patients with *Fanconi's anemia* (¶'s 146, 454). Leukemia occurred even in persons without the full Fanconi syndrome.

466. Schmid, Brecher, and Clemens reported on the cases of a 35-year-old man and his 11-year-old son with hemolytic anemia, inclusion bodies like Heinz-Ehrlich bodies in about a third of the erythrocytes, and excretion of dark brown pigments in the urine. Splenectomy was of no avail in either. The father died after a surgical attempt at relief of biliary obstruction due to gallstones. The son had an aplastic crisis, from which he recovered.

467. Martin, Kough, and Branche observed the combination of *hereditary spherocytosis* and sickle trait in 2 Negro sisters. The disease seemed no different in its clinical behavior from spherocytosis alone. A study of three generations

revealed 10 other individuals with isolated spherocytosis. (See also the report of Jones and Klingberg.) Metz described hereditary spherocytosis in the South African Bantu.

On the basis of 2 cases, Hellman and Davoodzadeh thought hemolytic crises in hereditary spherocytosis may be precipitated by pregnancy. In phlebograms, Piguet and Écoiffier demonstrated apparently congenital malformation of the leg veins in an 18-year-old girl with hereditary spherocytosis. They suggested that leg ulcers may be the result of such malformations and may occur, presumably, as a pleiotropic effect of the spherocytosis gene.

468. In both *pernicious anemia* and tapeworm anemia a marked increase in serum lactic acid dehydrogenase activity was observed during relapse. The enzyme decreased simultaneously with the reticulocyte peak (Gordin).

Neill and Weaver studied, in 17 patients with untreated pernicious anemia, four processes or products dependent on coenzyme A: (1) hippuric acid synthesis, (2) ability to acetylate a foreign amine, (3) blood cholesterol, and (4) blood cholic acid. The first and the third showed low values. It was suggested that the metabolic defect which is corrected by vitamin B_{12} may concern the synthesis of the lipid moiety of the lipoproteins of the erythrocyte membrane and of the central nervous system (¶464).

McIntyre and associates reported on a substantial study of the genetic predisposition to pernicious anemia (PA), by testing the ability to absorb orally given tracer doses of Co^{60}-vitamin B_{12} (Schilling's test). They studied 106 relatives of 34 PA probands and 97 healthy, control individuals with a negative family history for pernicious anemia and gastric carcinoma. The relatives of PA patients showed a negative regression with age; the normal, control individuals did not. The relatives as a group probably show bimodality for vitamin B_{12} absorption, although there is tremendous overlap and 2 or 3 more subjects in a single class (13.1 to 16.0 per cent) would cause the bimodality to disappear. The age trend may be responsible in part for obscuring the true bimodality. On the basis of the curve which showed suggestive bimodality, the authors chose 15.0 per cent or below as abnormal. The authors conclude that the main genetic predisposition to pernicious anemia is determined by a single autosomal dominant factor. Forty-eight per cent of siblings and 32.7 per cent of offspring of PA probands had abnormal absorption. Other hypotheses examined included (1) recessive inheritance, (2) homozygous dominant determination of pernicious anemia and heterozygous determination of low vitamin B_{12} absorption, and (3) polygenic inheritance. To test the last possibility as contrasted to simple dominant inheritance, they examined the proportion of affected persons of whose parents one, both, or neither was affected. If the trait is simple, relatively rare, and dominant, an affected person should have a single affected parent. With a polygenic trait, cases of affected offspring from 2 unaffected parents should occur frequently. Although the data were not sufficiently extensive to be completely conclusive, they suggest that the occurrence of affected offspring from 2 normal parents is rare. Another important demonstration was that the defect in vitamin B_{12} absorption is not dependent on achlorhydria. By study of one case of pernicious

anemia with onset in childhood, the possibility that such cases represent the homozygous state was disproved; both parents were normal although the father was in the low normal range. A feature of this case of childhood pernicious anemia was the association of hypoparathyroidism, reported by others in at least 2 cases in the literature. Manifestations of hypoparathyroidism had their onset at age 5; signs of typical pernicious anemia with severe subacute combined degeneration began at 12.

Thomsen investigated a possible relationship between macrocytic anemia of pregnancy and pernicious anemia. He estimated that macrocytic anemia occurs, in Sweden, in one of each 2,000 pregnancies, approximately. In one of 6 patients with macrocytic anemia of pregnancy, the mother had pernicious anemia. A family study by the methods of McIntyre and colleagues should be useful for determination of what relation there may be between these two diseases.

469. Chernoff reviewed the information on the distribution of *thalassemia.*

Bannerman, Grinstein, and Moore studied hemoglobin synthesis in thalassemia major by an in vitro technique by the use of samples of peripheral blood containing immature red cells. Heme synthesis was estimated by measurement of the amount of glycine-2-C^{14} or Fe^{59} incorporated into it in a given time under standard conditions and related to the absolute number of immature cells present. The results were compared with those observed in the blood of patients with other diseases with reticulocytosis. The estimate of heme synthesis based on labeled glycine was considered more valid than that based on Fe^{59}. A falsely low value for the latter probably resulted from dilution by the large iron stores characteristic of thalassemia. The authors concluded that heme synthesis in thalassemia is impaired in two ways: (1) by a relatively slow rate of protoporphyrin synthesis and (2) by a partial block in the combination of protoporphyrin and iron. Globin synthesis appeared to be normal.

Silvestroni, at the Centro di Studi della Microcitemia e delle Anemie Microcitemiche in Rome, has in the last 2 years observed 3 cases of microdepranocytic disease (S thalassemia), 6 cases of sickle cell anemia, 4 cases of H thalassemia, and 4 cases of "overflowing Hb A_2" microcythemic disease. The last condition is of particular interest and is newly described. The families he studied showed many individuals with high levels of Hb A_2, apparently as a genetic trait in heterozygous state. Among the offspring of parents, one with the high A_2 trait and one with the thalassemia trait, there were patients with both characteristics and with the clinical picture of severe Cooley's anemia. The heterogeneity of the category "thalassemia" is further indicated by the report by Aksov of cases of thalassemia minor that showed large amounts of fetal hemoglobin. Yet other evidence of heterogeneity leading to preference for saying "the thalassemias" is of several sorts: Kunkel and colleagues (1957) found that although the presumedly heterozygous parents of patients with thalassemia major usually show an increase of Hb A_2, a few do not. Families have been found in which the parents of patients with thalassemia major show no hematologic abnormality whatever.

Ingram developed the important hypothesis that the thalassemias are each due to a mutation producing a hemoglobin with a "hidden" amino acid

TABLE VI. INCIDENCE OF ABNORMAL HEMOGLOBIN IN SEVERAL LARGE GROUPS OF NEGROES

SERIES	NUMBER OF PATIENTS	AS SICKLE TRAIT		SS SICKLE DISEASE		S-C		AC C TRAIT		CC		OTHERS	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Smith and Conley	500	36	7.2	5	1.0	1	0.2	9	1.8	0		0	
Schneider	1,550	139	9.0	4	0.3	1	0.1	35	2.3	0		2*	0.1
Haynie and colleagues	400	36	9.0	5	1.3	1	0.25	6	1.5	1	0.25	0	
Chernoff	1,000	94	9.4	0		0		26	2.6	0		4†	0.4
Myerson, Harrison, and Lohmuller	1,000	74	7.4	3	0.3	2	0.2	23	2.3	0		4‡	0.4
Totals	4,450	379	8.5	17	0.4	5	0.1	99	2.2	1	0.1	10	0.2

From Myerson, R. M., Harrison, E., and Lohmuller, H. W.: Am. J. Med. 26:543, 1959.
*Two patients with thalassemia and increased Hb F.
†Four patients with Hb AD.
‡One patient with Hb AD and 3 with Hb F.

VOL. 12 1960

substitution, i.e., one without electrophoretic abnormality—the "substitution hypothesis." As other mechanisms for the low rate of normal hemoglobin synthesis in the thalassemias, he listed the following possibilities: (1) Defective enzyme might be present in a critical, rate-determining metabolic step in heme synthesis. If this were the case, the synthesis of fetal hemoglobin might be expected to be reduced. Actually, fetal hemoglobin is increased, possibly in compensation. (2) The switch-over mechanism from production of fetal hemoglobin to adult hemoglobin might be defective. Neither of these hypotheses would explain the fact that when the thalassemia gene is combined with the S or C hemoglobin gene the proportion of Hb S or C is about 80 per cent and most of the rest is fetal hemoglobin. This observation suggests that the thalassemia gene specifically inhibits the synthesis of Hb A with little or no effect on the synthesis of Hb S or C. Ingram analyzed several published pedigrees to indicate the agreement of observations with his substitution hypothesis. He postulates that there may be both α and β varieties of thalassemia, depending on which polypeptide chain (see ¶474) contains the substitution.

470. Stevens, Mackensen, and Bernstein described a new jaundice-anemia mutant in mice.

471. Mitus, Mednicoff, and Dameshek found high alkaline phosphatase activity in mature neutrophilis of 22 patients with *polycythemia vera* and virtually normal levels in persons with secondary polycythemia.

The hemoglobinopathies (Lehmann): *472.* General reviews included that of Beaven and Gratzer. Their review consisted, first, of an extensive analysis of methods and results of methods for separation and characterization of the hemoglobins and, second, of a discussion of all hemoglobins described up until early 1959. By this time the hemoglobins to which a letter of the alphabet had been designated reached Q and a number of others had been described but not fully characterized. Prins discussed the separation of human hemoglobins. Suarey and colleagues surveyed the incidence of abnormal hemoglobins in Puerto Rico. Myerson, Harrison, and Lohmuller provided a tabulation of the incidence of hemoglobinopathic conditions in 4,450 Negroes—a compilation of their own experience and that of four other groups (Table VI).

Under the editorship of Jonxis and Delafresnaye, a symposium dealing with abnormal hemoglobins in a very comprehensive manner and held in Istanbul in 1958 was published.

473. Hunt and Ingram reported that, rather than the amino acid sequence previously given (¶149) for these hemoglobins, the sequence in peptide 4 of Hb A and C and probably S is as follows:

Hb A. Val-His^{+}-Leu-Thr-Pro-*Glu*$^{-}$-Glu^{-}-Lys^{+}. . .

Hb S. Val-His^{+}-Leu-Thr-Pro-*Val*-Glu^{-}-Lys^{+}. . .

Hb C. Val-His-Leu-Thr-Pro-*Lys*$^{+}$-Glu-Lys^{+}. . .

The new schema indicates one fewer amino acid.

Hill and Schwartz presented evidence that the anomaly of Hb G is in the same peptide 4 of the β chain and that the sequence is as follows:

Hb G. Val-His^{+}-Leu-Thr-Pro-Glu^{-}-*Gly*-Lys^{+}. . . .

Note that the amino acid sequence worked out for peptide 4 has been modified from what was earlier thought to be the sequence (¶149). Peptide 4, obtained by tryptic digestion, appears to be the beginning of the β polypeptide chain of hemoglobin. Peptide 26 is inside the β polypeptide chain. Hunt and Ingram reported that in Hb E lysine is substituted for one of the glutamic acid moietices of peptide 26:

Hb A. . . . Val-Asp-Val-Asp^{-}-Glu^{-}-Val-Gly-Gly-*Glu*$^{-}$-Ala-Leu-Gly-Arg^{+}. . . .

Hb E. . . . Val-Asp-Val-Asp^{-}-Glu^{-}-Val-Gly-Gly-*Lys*$^{+}$-Ala-Leu-Gly-Arg^{+}. . . .

474. Singer and Itano (1958) showed that at pH 4.3 human hemoglobin splits into two unequal half molecules thought to represent α-α and β-β (Fig. 9). At neutral pH reassociation occurs. Vinograd, Hutchinson, and Schroeder did ingenious experiments making use of this type of reversible dissociation and showed that the α-α half molecules of Hb A and S are interchangeable, whereas the β-β ones are not. Thus, evidence that the mutational change in S involves the β chain was adduced. The same method has been applied to other hemoglobins (e.g., ¶' s 482, 490).

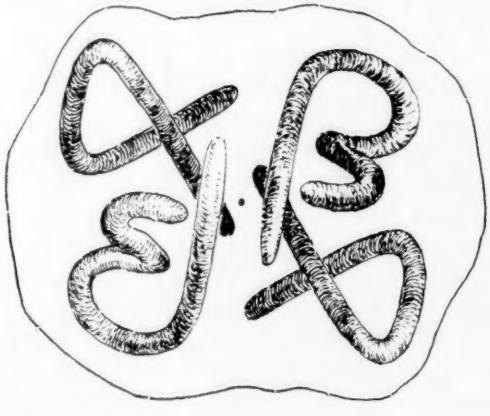


Fig. 9.—Schematic representation of the structure of hemoglobin with two α- and two β-polypeptide chains. (From Ingram, V. M.: Nature, London 183:1795, 1959.)

475. Two leading developments in medical genetics in 1959 were (1) the identification of chromosomal aberrations in several disorders (see ¶381 ff.) and (2) elaboration on the amino acid sequences and other structural details of the aberrant hemoglobins with particular reference to the significance of such studies for our definition of the gene. As stated by Ingram, the view has developed that separate, nonlinked genes specify the α and β chains of hemoglobin, that

the amino acid sequences are coded by particular nucleotide sequences in the DNA of the gene, and probably that secondary and tertiary structural characteristics of hemoglobin are a necessary consequence of the basic amino acid sequence.

TABLE VII. KNOWN ABNORMALITIES IN SOME HEMOGLOBIN VARIANTS*

	AFFECTED TRYPTIC PEPTIDE NUMBER	AMINO ACID ALTERATION
α Peptide Chain (Val–Leu–...)		
Hb Dα	23	?
Hb I	23	?
Hb Hopkins 2	?	?
Hb Q	?	?
Hb P	?	?
Hb J	?	?
β Peptide Chain (Val–His–Leu–...)		
Hb S	4	$Glu^{-} \longrightarrow Val$
Hb C	4	$Glu(1)^{-} \longrightarrow Lys^{+}$
Hb G	4	$Glu(2)^{-} \longrightarrow Gly$
Hb E	26	$Glu^{-} \longrightarrow Lys^{+}$
Hb Dβ	26	?
Hb L	?	?

*Courtesy of Dr. Vernon Ingram, Cambridge, Mass.

("Fingerprinting" of the hemoglobins and studies by acid dissociation and reassociation have provided much of the evidence on which the preceding view is based. The substitution theory of thalassemia advanced by Ingram and others is an extension of the same line of thought.) According to this view, all α-chain hemoglobin variants will be allelic and all β-chain variants allelic. The doctrine can perhaps be adequately stated as "one gene, one polypeptide."

The demonstration that Hb G is not only a β-chain variant but is, furthermore, the result of an amino acid substitution in the same peptide as in Hb S and C, at the position immediately adjacent to that substituted in Hb S and C, is disturbing to the doctrine outlined above, since Schwartz and colleagues in 1957 seemed to have demonstrated nonallelism of Hb G and S. (Fig. 10.) If the genes for Hb G and S were allelic, individual III 1 should have transmitted either one or the other to IV 1. Furthermore, the gene for Hb G must be nonallelic with that for thalassemia; otherwise, II 5 would not have transmitted both the Hb G trait and the thalassemia trait to III 1.

476. Lehmann has proposed a classification of hemoglobins into six groups according to their mobility on paper electrophoresis at pH 8.6 (Fig. 11). In fact, he proposes a system of nomenclature based on this. Hemoglobins which move identically at alkaline pH are at present differentiated by other methods, such as the following:

a. Electrophoresis at acid pH: H and I
b. Chromatography at pH 6: L, P, Lepore, Stanleyville I
c. Spectral analysis: M_B and M_S
d. Peptide analysis: D_α, D_β, D_γ

TABLE VIII. PROPOSED SYSTEM OF NOTATION FOR GENES AND THEIR PRODUCTS

	GENE NOTATION	GENE PRODUCT
Normal adult	Hb α^A/Hb α^A Hb β^A/Hb β^A	$\alpha_2^A \beta_2^A$ (Hb A)
Fetus	Hb α^A/Hb α^A Hb γ^F/Hb γ^F	$\alpha_2^A \gamma_2^F$ (Hb F)
Sickle cell trait	Hb α^A/Hb α^A Hb β^A/Hb β^S	$\alpha_2^A \beta_2^A$ (Hb A) $\alpha_2^A \beta_2^S$ (Hb S)
Sickle cell anemia	Hb α^A/Hb α^A Hb β^S/Hb β^S	$\alpha_2^A \beta_2^S$ (Hb S)
Hb I carrier	Hb α^I/Hb α^A Hb β^A/Hb β^A	$\alpha_2^A \beta_2^A$ (Hb A) $\alpha_2^I \beta_2^A$ (Hb I)
Double heterozygote Hopkins 2 and S	Hb α^{Ho^2}/Hb α^A Hb β^A/Hb β^S	$\alpha_2^{Ho^2} \beta_2^A$ (Hb Ho^2) $\alpha_2^A \beta_2^S$ (Hb S) $\alpha_2^A \beta_2^A$ (Hb A) $\alpha_2^{Ho^2} \beta_2^S$ (Hybrid Hb Ho^2/S)

Three loci are assumed—one for the α chain, one for the β chain, and one for the γ chain. The table is intended to be illustrative, not exhaustive. It is neither certain that the α chain of adult hemoglobin is identical with the α chain of fetal hemoglobin (¶480), nor that all "normal" adult Hb A is the same.

477. Hb C. Smith and Krevans presented pedigree evidence for the allelism of Hb S and C.

Sharpe and his colleagues reported on 5 Negroes with hematuria from hemoglobinopathic states: 3 were SC and 2 were SA. They emphasized unilateral bleeding—a feature which urologists ordinarily tend to consider an indication of surgical kidney disease.

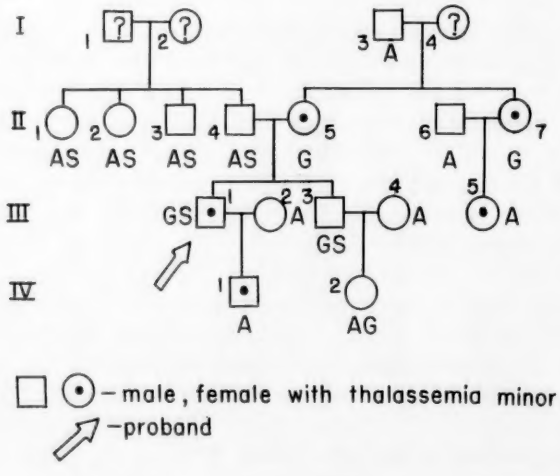


Fig. 10.—The pedigree reported by Schwartz and colleagues in 1957 is interpreted as indicating nonallelism of the genes for Hb G and S. In particular, individual IV 1 should have derived either Hb G or S from his father if the responsible genes were allelic.

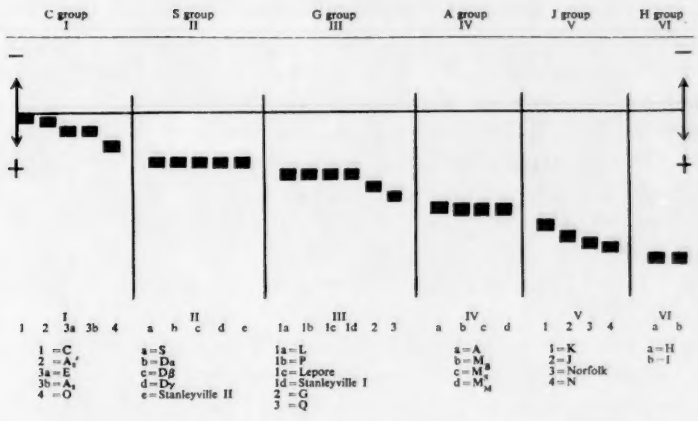


Fig. 11.—Pattern of mobility of adult hemoglobins on paper electrophoresis at pH 8.6. The named and lettered hemoglobins are accordingly indicated. M_B and M_S refer to the Boston and Saskatoon varieties of methemoglobin studied by Gerald and colleagues.

Smith and Krevans reported on 9 cases of C-C, 2 of S-C, and one of C thalassemia. In addition they analyzed 26 cases of C-C from the literature. By comparison with S-S, the impressive features of C-C include normal habitus and splenomegaly. The latter was present in 34 of 35 cases. They estimated that the Hb C trait occurs in 2 per cent of Baltimore Negroes. It is interesting that S-C disease displays features absent in SA, SS, CA, and CC states: typical retinal vascular changes, aseptic necrosis of the head of the femur suggesting Legg-Calvé-Perthes disease, and a high incidence of fatality during pregnancy that results mainly from fat and bone marrow embolism to the lungs and brain (Alper, Cavanagh, and Jonsson). Infarction of bone marrow with marrow embolism in S-C disease was also noted by Ober and associates and by Lau. Cases of S-C disease were also reported by Diamond. Sharpe and colleagues described unilateral renal bleeding and Alper, Cavanagh, and Jonsson described puerperal coma of sudden onset (resulting from embolism?) in cases of S-C disease.

In the Volta territory of West Africa, Sansarricq and colleagues found an unusually high frequency of homozygous Hb C disease (1.47 per cent) and concluded that this area is the epicenter for the gene. In 2,552 subjects, the findings were as follows:

AC	17 per cent	AS	5.8 per cent	AK	0.75 per cent	AG	3 cases
CC	1.47 per cent	SS	0.38 per cent				
SC	0.64 per cent						

In 73 per cent, the hemoglobin was judged to be AA.

Oehmann and Nuokolo suggested that the River Niger has been a barrier to the eastward spread of the gene for Hb C, just as the Zambesi River seems to have been a barrier to the southward spread of the gene for Hb S.

478. Hb D. Smith and Conley described a 21-year-old white male from North Carolina who had S-D disease manifested by bouts of jaundice and arthritis

in childhood, with hepatosplenomegaly and chronic anemia. Pain in the back was the main complaint at the time of the report and x-ray demonstrated "demineralization of the skeleton." Six of 11 paternal relatives had the sickle trait; 5 of 14 maternal relatives had the D trait. The differences between Hb S and D were reviewed. Arends, Layrisse, and Rincon described S-D disease in a 14-month-old Portuguese child with severe hemolytic anemia. The father had the Hb D trait; the mother had the sickle trait.

Silvestroni, Bianco, and Muzzolini found a 44-year-old man with Hb DA in a survey of 2,186 persons in southern Italy. Five relatives were also heterozygous for D. Intracorpuscular crystallization of hemoglobin was easily demonstrated in all.

Electrophoresis of hemoglobin in agar gel separates fetal hemoglobin from adult hemoglobin and Hb D from sickle hemoglobin. In reviewing 400 cases which, according to paper electrophoresis, were presumed to be SA cases, Marder and Conley found 4 cases of DA (a frequency of the DA trait of 0.085 per cent). Review of 91 cases of "SS" revealed no case of SD.

479. Hb E. Discovered by Itano, Bergren, and Sturgeon (1954), Hb E is one of the major hemoglobin variants; it is especially frequent in Southeast Asia. As in Hb S and C, the anomaly concerns the β chain. However, the anomalous amino acid substitution is in peptide 26, not peptide 4 as in Hb S and C (¶473). Hunt and Ingram reported that lysine is substituted for one of the glutamic acid moieties of this peptide. It will be noted that although different peptides are involved, the same amino acid substitution has occurred as in Hb C; the electrophoretic behavior of Hb E and C is similar. The only family in which E has occurred in association with another abnormal hemoglobin (S) is that reported by Aksoy and Lehmann (Nature, London 179:1248, 1957). This pedigree suggested allelism or close linkage of the two factors. The evidence from Hunt and Ingram in the frame of reference of the present concepts—that a particular strand of desoxyribonucleic acid is responsible for the β chain and that different peptides in the β chain are determined by different parts of this strand (¶475)—would suggest that E and S are closely linked but not allelic.

Van Dijk described 2 patients with the clinical picture of Cooley's anemia. Of each, one parent showed the thalassemia trait and one was heterozygous for Hb E. Each of the patients showed only Hb E and F. Lie-Injo, Hoo, and Kho pointed out that Hb E–thalassemia disease may vary in severity from a severe disease requiring repeated blood transfusion to a totally asymptomatic trait. They described exacerbation of the disease by pregnancy with two premature births and one neonatal death.

480. Hb F. Naylor and Adair reported on the serologic, i.e., immunologic, differences between adult and fetal human hemoglobin. Beaven and Gratzer studied the fetal hemoglobin of the monkey.

Tuchinda and colleagues collected cord blood from 415 Thai babies; 22 (5.2 per cent) contained an electrophoretically "fast"-moving component. No other abnormal hemoglobin was found. An incidence of 10 per cent Hb E,

the only abnormal hemoglobin, was found in the 412 mothers. The abnormal hemoglobin may be a variant of fetal hemoglobin and may be identical to "Bart's" hemoglobin of Lehmann. Boyo and Hendrickse found a "fast hemoglobin" in 15 of 150 newborn Nigerians including a pair of monozygotic twins.

In 1958 the group at St. Bartholomew's Hospital, London (Ager and Lehmann) and that at the Alexandra Hospital, Athens (Fessas and Papaspyrou) reported on two variants of fetal hemoglobin. Both were "fast" hemoglobin, that is, on paper electrophoresis at alkaline pH they moved toward the anode faster than Hb A; the two were apparently different. The English one was termed fetal variant "Bart's." In 1959 the same two groups (Fessas, Mastrokalos, and Fostiropoulos; Vella, Ager, and Lehmann) described a third fetal hemoglobin variant. This hemoglobin shows less anodic mobility than Hb F and A. The Greek group suggested the tentative designation of fetal hemoglobin "Alexandra."

In Singapore, Vella found the incidence of the three fetal hemoglobin variants shown in Table IX.

TABLE IX. VARIANT FETAL HEMOGLOBINS IN SINGAPORE

ETHNIC GROUP	N	TYPES		
		FESSAS-PAPASPYROU	BART'S	ALEXANDRA
Chinese	1,962	63	2	8
Malay	162	2		2
European	142	1		1
Indian	222	2		
Eurasian	10			1
Nepalese	19			
Totals	2,517	68	2	12

From Vella, F.: Nature, London 184:272, 1959.

Normal fetal hemoglobin consists of two kinds of polypeptide chains called (1) "α," because it is seemingly identical to the chain similarly termed in adult hemoglobin and (2) "γ," a unique chain (Hunt). Hunt and Lehmann reported that Hb "Bart's" contains no α chains. It appears to be composed of four γ chains associated in a tetramer. The molecular weight is about 68,000. Hb "Bart's" is a counterpart of Hb H, which is a tetramer of only β chains. The blood picture of infants with Hb "Bart's" (especially the presence of "target cells") is similar to that of thalassemia; however, the change does not persist into adult life. The fact that α chains are formed for adult hemoglobin but not for fetal hemoglobin in the case of "Bart's" may indicate, although not necessarily so, that fetal α and the adult α are determined by different genes and are fundamentally somewhat different despite failure up to this point to demonstrate any difference.

Halbrecht, Klibanski, and Bar Ilan presented further work purporting to demonstrate an embryonic or primitive hemoglobin which antedates fetal hemoglobin in ontogeny.

481. Hb G. See ¶'s 473, 475.

482. Hb H. Jones, and associates showed that Hb H contains only β chains associated in a tetramer. Peculiar physical properties of the β tetramer are presumably responsible for the inclusion bodies present in the erythrocytes in cases of Hb H disease (¶153). Hb H is found only in the presence of a gene for thalassemia. Thus far, α_4^A, i.e., hemoglobin containing only "normal" α chains, has not been identified. As noted above, "Bart's" fetal hemoglobin is γ_4^F.

Ramot and coauthors described a 40-year-old oriental Jewess who had Hb H, persistent Hb "Bart's" (see ¶480), thalassemia minor, and primaquine-sensitive erythrocytes. One daughter also had Hb H and persistent Hb "Bart's." Since Hb "Bart's" is a tetramer of γ chains and Hb H a tetramer of β chains, they suggested that one genetic defect affecting the α chains is operative in these cases. If the α chains of Hb A and F are identical, one would expect to find Hb H in adults and Hb "Bart's" in infants. The fact that this is not the case suggests that genetic control of the formation of α chains is independent in infants and adults. However, in the specific instance at hand the α-chain defect appeared to be a quantitative one. Hb A was still the predominant component, representing about 80 per cent. Furthermore, the fact that none of three other children of the proposita inherited one of the defects singly suggests that only a single α-chain defect was involved.

483. Hb I. Murayama and Ingram found that the amino acid substitution of Hb I involves the twenty-third peptide of the α polypeptide chain. Itano and Robinson found that normal hemoglobin (and doubly abnormal hemoglobins) could be found by recombination of the acid-dissociation products from Hb I, on the one hand, and Hb S or C on the other—support for the view that the α chain contains the anomaly in Hb I, whereas the anomaly in S and C resides in the β chain. Normal hemoglobin is produced from combination of β dimers from I with α dimers from S or C.

484. Hb J. Went and MacIver described a case of SJ disease resulting in a "mild well-compensated hemolytic anemia with target cells." The Hb S gene came from the Negro mother; the J gene apparently came from a Caucasian American citizen "of fair complexion."

485. Hb K. Cabannes and Portier presented a family in which Hb A, one Hb D, and Hb K were segregating independently.

486. Hb L. Sukumaran and colleagues described Hb L in three Gujarati-speaking Lohana families in Bombay. This hemoglobin has been described only in India. All affected persons in the three families were heterozygotes.

487. Hb M. Gerald and George studied the methemoglobin in a Canadian family with dominant inheritance of methemoglobinemia. They found an abnormal hemoglobin (called by them "M_S" for Saskatoon) distinct from the

VOL. 12 1960

abnormal hemoglobin (called "M_B") in the Boston family with dominantly inherited methemoglobinemia. Starch block electrophoresis and absorption spectra displayed differences. The forms of hereditary methemoglobinemia which are due to enzyme defects are inherited recessively.

488. Hb P. Dherte, Lehmann, and Vandepitte described Hb P in a family in the Belgian Congo. One member had three different hemoglobins, S, A and P, suggesting that Hb S and P are not determined by alleles. Whereas S and C are allelic (Ranney and colleagues, 1953), S and G seem to be nonallelic (Schwartz and associates, 1957), as do also S and Hopkins 2 (a fast hemoglobin, ¶156) and one form of D and K (Cabannes and Portier).

489. Hb S. (See also ¶'s 473 to 488.) Choremis and co-workers studied the aminoaciduria of sickle cell anemia and thalassemia and concluded that there is reduced reabsorption of amino acids from the glomerular filtrate.

Raper extended the observations on the interaction of sickling and malaria. In Africa in a survey of children all heavily exposed to natural infection with *Plasmodium falciparum*, he found that the degree of parasitemia was inversely related to the Hb S content of the erythrocytes, as indicated by the division of the children into three groups, AA, AS, and SS. Ogden quoted Bangham (Nature, London, 1958) as suggesting that certain bovine hemoglobin types endow cattle with a relatively high tolerance to trypanosomiasis.

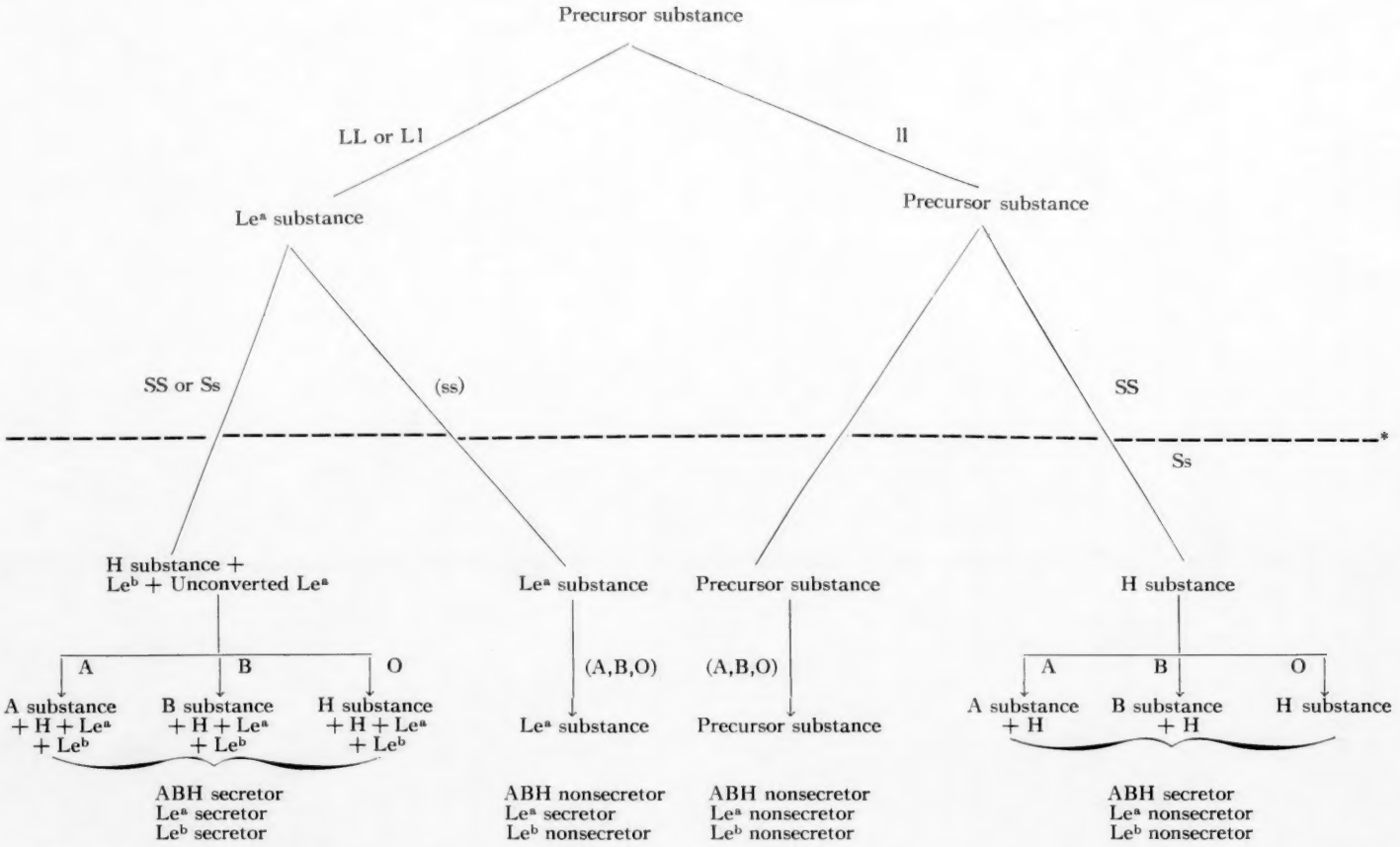
Ray, Cassell, and Chaplin studied the behavior of stored red blood cells from individuals with the sickle cell trait. Because the frequency of sickle heterozygotes is 8 per cent or higher among American Negroes, the characteristics of transfused bank blood from such persons is of considerable significance. These workers could demonstrate no significant abnormality in terms of red cell survival.

Henderson and Gray added boxing to high altitude flying in the list of activities to be avoided by persons with the sickling trait. Renal injury, which is an occupational hazard, is likely to initiate bleeding from a kidney, a complication which can occur even without trauma (¶477).

Henderson, Crockett, and Wright could demonstrate no effect of carbonic anhydrase inhibitors on sickling, red blood cell count, or sedimentation rate in 4 cases of sickle cell anemia. Dos Santos and Lehmann and also MacDougall and Jacob were unable to convince themselves that acetazolamide (Diamox) has any beneficial effect in sickle cell anemia.

490. Other variant hemoglobins. Two new variants of adult hemoglobin tentatively called by the authors "Stanleyville I and II" were described by Dherte and associates. Schneider and Haggard found a hemoglobin in Galveston that behaved similarly to Stanleyville I. A hemoglobin which may be "new" was described by Gillespie and coauthors.

Itano and Robinson showed that Hb Hopkins 2 is an α-chain variant. This evidence is consistent with the demonstration of nonallelism of Hb S and Hopkins 2 by Smith and Torbert (¶156).



*Level of action of the xx Bombay genotype.

Fig. 12.—The Watkins-Morgan schema of the genetic pathways in the biosynthesis of blood group mucopolysaccharides.

VOL. 12 1960

Polymorphic hemoglobins have now been demonstrated electrophoretically in many vertebrates other than man, including sheep, horses, goats, mice (¶66), and fish (Hashimoto and Matsuura).

Tamura and colleagues described "hereditary black blood disease," as an autosomal dominant trait, with 35 affected members in five generations of a Japanese family. The disorder has seeming similarities to methemoglobinemia, but the black color of the blood may be more pronounced since some of these cases have been reported as "hereditary Addison's disease." The characteristic color of the skin and mucous membranes is observed from birth and never changes throughout life. No clinical or other (e.g., anthropometric) abnormality accompanies it. The oxygen-combining capacity of the blood is normal. The nature of the discoloring substance has not been identified, but the authors suggest that there may be an abnormal structure of heme, specifically of the porphyrin nucleus. In the broadest sense it is, then, a genetic hemoglobinopathic condition. A striking increase in urinary excretion of xanthuren was demonstrated. This hemoglobin variant would appear to be the first in which the peculiarity resides in the heme part of the molecule.

L.
2
60

Blood Groups.—

491. Watkins and Morgan made an important contribution to the concepts of the genetic pathways involved in the formation of blood group mucopolysaccharides. Their concept synthesizes many observations concerning the genetics and biochemistry of the ABO system, the Lewis system, and the secretor trait. Among the chemical observations are the following:

a. There is a striking similarity in the qualitative chemical composition of the blood group substances irrespective of the individual from whom they were derived.

b. The A, B, and H substances after mild degradation and the untreated "inactive substance Fl" and Le^a substance cross react with type XIV *Diplococcus pneumoniae* antiserum.

c. Certain enzymatic treatment of A and B substances results in the appearance of H activity.

d. Multiple specificities can be demonstrated on the same mucopolysaccharide molecule.

e. Some information is available about the chemical structure responsible for the particular blood group specificities.

Among the genetic observations taken into account in construction of the Watkins-Morgan schema (and the modification shown in Fig. 12) are the following:

a. There are three genetically independent but phenotypically interacting loci involved in ABO, Lewis, and secretor characteristics.

b. There is a locus called "Bombay" (the alleles are called "X" and "x") which when homozygous (xx) suppresses the formation of ABO-specific chemical structure in the mucopolysaccharide molecule.

c. There is another locus at which the alleles are referred to as "Y" and "y" which when homozygous (yy) suppresses the formation of A-specific chemical structure in the mucopolysaccharides.

d. There is an interaction of the Lewis system and secretion of ABH which was schematized by Ceppellini as shown in Table X.

492. Brown, Glynn, and Holborow studied Le^a substance in saliva by means of a precipitin test using rabbit anti-Le^a serum. In nonsecretors the Le^a substance was precipitated, but not in secretors. They suggested that the results are explained by the presence in saliva of a blood group substance macromolecule which in secretors has much ABH and fewer Le^a specific groupings on its surface. In secretors a majority of the surface sites are thought to be usurped by ABH groupings. According to Grubb and Ceppellini, roughly 90 per cent of both secretors and nonsecretors have Le^a antigen in their saliva, the character being distributed independent of the secretor character.

VOL. 12 1960

493. Giblett and Chase may have discovered an eleventh blood group system which they proposed to call "Sutter" for a patient who generated the antiserum used in their study. J. S. was a young white male who received blood from a Negro donor in connection with a surgical operation for lung cancer. On subsequent cross matching, his serum was found to agglutinate cells from certain Negro donors. The antigen designated "Js^a" is present in about 20 per cent of Negroes. Presumably Js^b will be discovered in due course. The workers satisfied themselves that the antigen is not in any of the following well-known systems:

ABO	Duffy
MNSs	Kidd
Rh	Diego

They doubt that it is in one of the following systems:

Kell	Lutheran
P	Lewis

(Layrisse, Sanger, and Race, studying families from hybrid populations in Venezuela, likewise demonstrated that Js^a is independent of Duffy, Kidd, Diego, MNSs, and Rh.)

The authors point out that other antigenic peculiarities of the Negro include a relatively high incidence or unique occurrence of cDe; the Rh antigen V; Hunter, Henshaw, and S^u of the MNSs system; and failure to react with either anti-Fy^a or anti-Fy^b of the Duffy system. Interracial blood transfusions may reveal other erythrocyte antigen systems. Layrisse and de Layrisse found a very low frequency of Js^a in South American Indians and suggested that the antigen might be useful in studying Negro gene flow into hybrid populations.

494. Cleghorn also discovered a "new" human blood group antigen in the red cells of a man named Swann and proposed to call it "Sw_a." Tests of 29,487 random blood samples revealed four more Sw_a-positive individuals. Two samples were from related persons. Studies in three families revealed that Sw_a is inherited

as a Mendelian dominant character which segregates independently of ABO, Rh, MNSs, Kell, Lewis, Duffy, Kidd, and ABH secretion. The new blood group must be unusual in that it has been named for the first person discovered with the antigen, not the antibody. His antigen was discovered during the course of compatibility tests preparatory to transfusion in a patient with autoimmune hemolytic disease.

TABLE X. CEPPELLINI'S SCHEME OF THE LEWIS SYSTEM AND ABH SECRETION

GENOTYPE	SALIVA			RED CELLS
	ABH	Le^a	Le^b	
SSLL SSLl SsLL SsLl	+	+	+	Le(a − b +)
ssLL ssLl	−	+	−	Le(a + b −)
SSll Ssll	+	−	−	Le(a − b −)
ssll	−	−	−	Le(a − b −)

495. Kortekangas and colleagues reported on a second family with the rare red cell antigen P^K, which is of genetic interest because the P system is not inherited as a completely straightforward dominant character. In the reported family neither parent of a P^K individual possessed this antigen. To the minds of these workers, the most likely hypothesis is that P^K is determined by a gene which can express itself only in the absence of P_1 and P_2, i.e., in the genotypes P^Kp or p^Kp^K. This family lived in Finland; the only previously reported family was of Finnish descent, living in Minneapolis. P^K persons have naturally circulating anti-P comparable to anti-A and anti-B of the ABO system.

496. Weiner and Unger reviewed recent discoveries in the Rh system, together with clinical problems associated with newly discovered antibodies. Sacks and colleagues described isosensitization to a new blood group factor, Rh^D, in the Rh system.

Weiner reported on two kidnapping cases in which blood groups were used to settle the issue of disputed maternity. In one case the kidnapper was type Rh_2Rh_2 and the baby type Rh_1Rh_1. In the second case the kidnapper was A_2B and the baby group O. The kidnapper in the second case had been previously grouped incorrectly as B. A_2B is frequently misclassified B. Weiner discusses qualifications for an expert witness in cases of disputed parentage. He questions whether many of the some 200 persons who have registered with the College of American Pathologists as willing to act as consultants in such cases are actually fully qualified to do so.

In 320 families in which hemolytic disease had occurred and in which the paternal genotype was known, Kirk, Vos, and Kelsall could find no difference in

the severity of hemolytic disease according to whether the father was R_1R_1 or R_1r rather than R_2R_2 or R_2r. The results contradict those of Murray (1957).

Krivit and colleagues presented evidence for fetomaternal transfusion, the transfer of appreciable amounts of blood from the fetus to the mother, a matter of obvious pertinence with reference to hemolytic disease of the newborn. The evidence of fetomaternal transfusion was threefold: (1) direct agglutination of fetal erythrocytes in the mother's blood, (2) an increase of fetal hemoglobin in the mother's blood, and (3) a rising anti-D titer in the mother.

497. Metaxas and colleagues found another case with anti-Lu^b antibody—probably only the third example discovered to date. They were able to get further evidence for the Lutheran-secretor linkage as described by Mohr (1954) and corroborated by Sanger and Race (1958). Combining the data of Sanger and Race and that on two families found by Lawler and Renwick (¶504) with their own, the authors calculated a recombination fraction of 0.13.

VOL. 12 196

498. Studying the Diego blood group system, Mallén and Arias found $Di^a(+)$ in 20.39 per cent of Mexican Indians. Analysis of 30 Indian matings with a total of 62 children supports the hypothesis that the Diego antigen is determined by a gene capable of expression in either the homozygous or heterozygous state. Study of the Diego antigen began in 1954 when Levine and colleagues found the corresponding antibody in the blood of a Venezuelan woman whose baby had hemolytic disease. The Diego factor has proved of great anthropologic interest because it is very rare in Caucasoids, has never been found in Negroes, Australian aborigines, and Polynesians, but occurs in Mongoloids in percentages ranging from 5 (in Chinese of Canton) to 45.8 (in certain Brazilian Indians). In 1955 anti-Di^a was found by Levine to be responsible for hemolytic disease in a Polish family living in Buffalo, New York. The known permeation of Mongoloid peoples into eastern Europe makes the finding not surprising. Tatarsky and coauthors reported on another example of anti-Di^a from a family bearing a Spanish name and living in the Dallas area of Texas. Indian admixture was denied by the father but is entirely likely.

Associations of blood groups with disease; blood groups and selection: (See also ¶'s 327, 433.) *499.* Buckwalter and colleagues found a significantly increased incidence of blood type O in 2,370 patients with psychoses and a significantly increased evidence of blood type A in 565 patients with intracranial neoplasms. Nordmo could find no deviation in ABO or Rh blood groups in patients with schizophrenia or mental deficiency but did find an association between alcoholism and blood group A which was statistically significant at the 0.004 per cent level. Sievers and Calabresi found a slight excess of blood group O in persons with polycythemia vera.

White and Eisenberg found a more impressive excess of A individuals in males with cancer of the pylorus than in females or in patients with cancer arising in other parts of the stomach. Barber and Dunsford found an excessive amount

of blood group substance A in the serum of a patient with widespread metastases from carcinoma of the cardia of the stomach. Because of the association between carcinoma of the stomach and blood group A, the possibility that the carcinoma was producing A substance or was induced as a result of the high A substance should be considered. On the other hand, the finding may have been only fortuitous.

500. It has been recognized in recent years that maternal-fetal incompatibility in ABO blood groups is a factor in fetal and neonatal deaths (Matsunaga, 1953 ff.; Levine; Cohen and Glass). Since the eliminated individuals represent only part of the heterozygous concepti incompatible with the mother in respect to blood groups, there may be factors, either genetic or environmental, influencing the development of maternal-fetal isoimmunization, or the course if such immunization occurs. A suggestion of an environmental effect was implicit in a comparison of the mortality rates of heterozygotes estimated at about 21 per cent by Matsunaga and Itoh (1958) in a very poor mining area in Japan and about 7 per cent by Reed (1956) using data of Kirk and colleagues from a population with a higher standard of living in Australia. Haga, of Matsunaga's department, studied a mining district near that studied by Matsunaga and Itoh but with much better living conditions. The mean number of pregnancies per woman was the same in the two groups, but miscarriages and stillbirths were much less in the population with better environment—5 per cent as compared to 12 per cent. Using the new data, the mortality rate due to ABO heterozygosity was estimated at 5 per cent, a great difference from the 21 per cent estimated for the other group.

Reed and Ahronheim found in a study of 558 matings of white Protestant persons that fertility was significantly greater in ABO incompatible matings (those in which the husband had an agglutinogen that was lacking in the wife) than in compatible matings. The biologic interpretation of these results is not evident, especially since in Rh compatible matings the increased fertility of the ABO incompatible individual was still evident.

501. Allan found that the sex ratio (M/F) was higher for babies born to mothers of blood group AB than those born to O, A, and B mothers combined (1.26 versus 1.08). The sex ratio of O babies born to O mothers is significantly higher than that of A babies born to A mothers (1.11 versus 1.02). The sex ratio among O babies is higher than that among A babies (1.11 versus 1.03). If the sex ratio at conception is much higher than that at birth, any factor favoring survival of the fetus will raise the sex ratio.

502. Joysey, Goodwin, and Coombs described investigation of hemolytic disease in newborn pigs. The blood group antigen-antibody systems responsible have been worked out to a considerable extent.

503. Anthropologic studies of blood groups included those of Sussman and colleagues in the Marshall Islanders and Beckman and colleagues in the Swedish Lapps.

504. The May, 1959, issue of the *British Medical Bulletin* was devoted to a series of papers on blood groups, all of which have genetic interest. The individual contributions were as follows:

a. Mollison, P. O.: Relative Importance of Blood-Group Antibodies.

Many naturally occurring antibodies, including the natural blood group antigens, are found in the "19S" component of γ globulin, whereas immune blood group antibodies tend to be confined to the "7S" component (Kunkel and associates, 1958).

b. Race, R. R., and Sanger, R.: The Inheritance of Blood Groups.

These and at least one other writer in this series pointed out that, although in the restricted sense blood groups include only the differences due to antigens of the red cells, in the broader sense the different hemoglobins, haptoglobins, γ globulins (Gm groups), and β globulins are blood groups. They provided the table reproduced here as Table XI.

VOL. 12 196

TABLE XI. BLOOD GROUP ANTIGENS IN MAN

SYSTEM	ANTIGENS DETECTED BY	
	POSITIVE REACTION WITH SPECIFIC ANTIBODY	POSITIVE REACTION WITH ONE ANTIBODY, NEGATIVE WITH ANOTHER
A_1A_2BO	A_1, B, H	A_2, A_3, A_x
MNSs	M, N, S, s, Mi^a, Vw, Hu, He, M^g, Vr	M_2, N_2, M^c
P	P_1, P^k	P_2
Rh	D, C, c, C^w, C^x, E, e, E^w, f, V	D^u, C^u, c^v, E^u
Lutheran	Lu^a, Lu^b	
Kell	K, k, Kp^a	
Lewis	Le^a, Le^b	
Duffy	Fy^a, Fy^b	
Kidd	Jk^a, Jk^b	
Diego	Di^a	
Sutter	Js^a	
"Private"	Levay, Becker, Ven., Wr^a, Be^a, Rm, By	
"Public"	Vel, Yt^a, I	

From Race, R. R., and Sanger, R.: Brit. M. Bull. 15:99, 1959.

The discussion of the MNSs system is particularly complete and illustrates the usual course of development of information about a given system. It appears that the MN locus and the Ss locus are either very closely linked (no crossing over between them has ever been proved) or are part of the same gene with each part retaining an independent capacity for substitution. ". . . Geneticists do not agree on how to define the boundaries of a gene."

How one establishes that a newly discovered antigen represents a new system is discussed. In essence the argument is based on independent segregation of the newly discovered gene with regard to the genes for the established blood group system. As in all linkage studies the test is laborious.

It is difficult to be certain about mutation of blood group genes, that is, mutation in the generations observed. Illegitimacy and confusion of infants must be excluded. A possible instance of blood group mutation is that reported by Henningsen and Jacobsen (1954): an N child was born of an MM mother.

Many genetic principles known from other forms of life have been illustrated by findings in blood groups: (1) The interaction of alleles. Two M genes produce more antigen than does one M gene. (2) The interaction of genes at separate loci. The secretor locus, of course, controls whether the ABO gene expresses itself in the saliva. Another fascinating example is that of the Xx genes, and the "Bombay" phenomenon. The xx genotype is accompanied by suppression of ABH antigen. Another common modifying gene, locus Yy in the yy genotype, suppresses development of A antigen on the red cell but B and H are not affected. The interaction of Lewis and secretor is yet another example. The antigens Le^a and Le^b are primarily antigens of the body fluids, especially of the saliva, and only secondarily become attached to the erythrocyte. According to the present interpretation of findings, "There is a limited amount of substrate that can be made into water-soluble ABH substance or Le^a substance. The demands of the secretor and ABO genes are satisfied first and consequently, in secretors little substrate is left for the L gene to make into Le^a substance, some Le^a substance does reach the saliva but not enough reaches the plasma to hook on to the red cells and make them give the Le(a+) reaction. In non-secretors, however, all the substrate is available for the L gene to mold into Le^a substance; then the saliva is saturated with Le^a substance and enough reaches the plasma to hook on to the red cells and make them give the Le(a+) reaction."

The authors point out that with minor qualifications blood group antigens behave like straightforward dominant characters. No good example has yet been found of a recessive antigen, that is, an antigen which for its appearance requires the presence of an allele in double dose.

c. Morgan, W. T. J.: Some Aspects of the Biochemistry of the Human Blood-Group Substances.

d. Coombs, R. R. A.: The Antiglobulin Reaction.

e. Roberts, Fulton: Haemolytic Disease of the New-born.

Interesting notes on the history of familial neonatal jaundice in infants proved to have patent biliary tract are provided (Pearson, 1799; Cheyne, 1802). In the mule-breeding areas of France, Italy, and Spain, the disease was called "pissement de sang" from the hemoglobinuria and "l'ictère de poulain" from the jaundice. The greater antigenic differences of the mare and donkey account for a high incidence of hemolytic disease in the newborn mule. Suckling in the first days of life is an important factor in the equine and porcine species; large amounts of blood group antibody are contained in the colostrum and absorbed by the immature alimentary tract. The finding of Cremer, Perryman, and Richards (1958) that exposure of the erythroblastotic infant to sunlight reduces the bilirubinemia is cited.

f. Walker, William: The Management of Haemolytic Disease of the New-born as a Community Problem.

The following figures on the relative significance of ABO sensitization are cited: 16 of 290 cases of neonatal hemolytic disease (5.5 per cent) were due to ABO incompatibility; 8 of 627 deaths from hemolytic disease (1.3 per cent) had had this basis.

g. Roberts, J. A. Fraser: Some Associations Between Blood Groups and Disease.

The reality of the associations is defended. Duodenal ulcer is commoner in persons of group O. Cancer of the stomach is commoner in persons of group A. There is some increase in stomach ulcer in persons of group O. In pernicious anemia, the evidence for an excess of A is very strong. The evidence for an excess of A in diabetes mellitus is "fairly strong." The association of nonsecretor and duodenal ulcer is even stronger than the association of O and ulcer. Two investigations have shown an excess of group A in uterine cancer. Many negative findings, with reference to other diseases, are cited, as well as studies which have yielded contradictory results.

Fraser Roberts pointed out that a good way to indicate association is by simple cross multiplication, which expresses the incidence of disease in persons of one group in terms relative to the incidence in another group (¶327). For example:

	O	A
Peptic ulcer patients	535	311
Control subjects	4,578	4,219

$$\frac{535 \times 4{,}219}{311 \times 4{,}578} = 1.59$$

In this experience blood group O was 1.59 times as frequent in peptic ulcer patients as in controls.

h. Sheppard, P. M.: Blood Groups and Natural Selection.

What is known about the factors responsible for the blood group polymorphism is reviewed.

i. Mourant, A. E.: Blood Groups and Anthropology.

j. Lawler, Sylvia D., and Renwick, J. H.: Blood Groups and Genetic Linkage.

Three autosomal linkages have a recombination value of 10 per cent or less:

Lutheran: secretor	7.5 per cent (Mohr, 1951)
One elliptocytosis locus: Rh	3.3 per cent (Lawler, 1954)
Nail-patella: ABO	9.7 per cent (Renwick and Lawler, 1955)

A plea is made for publication of full pedigree data and for the central recording of identifying information on families so that further generations can be studied in the future.

It is to be hoped that studies of the human chromosomes and the aberrations therein will permit one to relate genes to a specific autosomal chromosome. In man all one can do is delineate linkage groups. The only mammal in which specific localization has been at all possible is the house mouse; phenotypic abnormalities have been correlated with microscopically visible aberrations of the chromosomes (Nature, London 174:309, 1954).

k. Glynn, L. E., and Holborow, E. J.: Distribution of Blood-Group Substances in Human Tissue.

The associations of blood groups and disease render studies of this sort particularly pertinent.

l. Sneath, Joan S., and Sneath, P. H. A.: Absorption of Blood-Group Substances From Serum on to Red Cells.

The discussion concerns mainly the Lewis system. The R system of sheep and the J system of cattle also consist of antigens located primarily to the body fluids and only secondarily to the erythrocytes.

m. Joysey, Valerie C.: The Relation Between Animal and Human Blood Groups.

Not only red cell antigens but also serum protein and hemoglobin types are discussed.

n. Bird, G. W. G.: Haemagglutinins in Seeds.

The biologic significance of the presence of agglutinins in seeds is obscure. Botanists have concerned themselves rather little with the phenomenon. More information on the genetics of the agglutinins would be of considerable interest; breeding of plants to produce more specific agglutinins, such as an exclusively specific anti-B, could have practical value.

Brief biographic sketches of the contributors are included at the end.

Miscellaneous.—

505. Hsia, Naylor, and Bigler reported *Gaucher's disease* in father and son and reviewed the literature for evidence of forms of the disease, the biochemical nature of the basic defect, and the mode of inheritance. The survey of the literature involved 110 families. The authors suggested that the entity characterized by the presence of Gaucher cells may in fact be three distinct entities: "In a few families, the condition is transmitted by an autosomal dominant gene; in the majority, it is caused by an autosomal recessive gene; and, in a third group, there is always neurologic involvement in addition to the usual changes in the bone, liver and spleen, and the condition also appears to be transmitted as an autosomal recessive gene." Greenwald and Fenton observed normal pregnancies in 3 women with Gaucher's disease. Bernstein and Sheldon found Gaucher cells in the newborn sibling of a patient known to have Gaucher's disease. Tuchman, Goldstein, and Clyman studied the high acid phosphatase of Gaucher's disease. They found that the acid phosphatase has the following atypical features: it is high using disodium phenylphosphate as substrate and is not inhibited by l-tartrate, formaldehyde, or copper.

XI. CARDIOVASCULAR SYSTEM

506. Phillips and Burch compared the natural history of cardiovascular diseases in the white and Negro races. In their introduction they reviewed seventeen factors which must be considered in interpreting any study of racial relationships in disease. A valuable resumé of evidence on Negro-white differences in the four major varieties of cardiovascular disease as well as others was provided.

McKusick reviewed genetic factors in cardiovascular diseases. Whenever one undertakes to analyze the role of heredity in diseases of a particular system,

one finds that disorders tend to fall into two major categories: (1) the common diseases which are often of multifactorial causation and in which the genetic factors are complex and (2) multiple, individually rare, disorders of more strictly Mendelian etiology. This dichotomy was used in the review referred to.

507. Hypertension. The studies of Pickering and colleagues led them to the conclusion that the frequency distribution for blood pressure is "continuous," that the genetic determination of blood pressure is polygenic, and that essential hypertension is not a discrete disease but rather is the state found in persons at the high end of the continuous distribution. Two analyses reported in 1959, one by Platt of Manchester and one by Morrison and Morris of London, seem to indicate a bimodality consistent with the view that a single "dominant" gene is a significant factor in hypertension.

Platt reanalyzed the data of Pickering and his colleagues and of Søbye. The blood pressure of hypertensive probands and their siblings aged 45 to 60 years was used since (1) this could be expected to exclude a certain number of cases of secondary hypertension which in Platt's experience is more frequent than essential hypertension under the age of 40 years and (2) the necessity for age correction is avoided. A bimodality was clear for systolic pressures and suggestive for diastolic pressures. Platt pointed out that if hypertension affects about 19 per cent of middle-aged persons (figure chosen in part for convenience) and that if hypertension is a simple dominant trait, the incidence of the three genotypes becomes as follows:

$$q^2 = 0.81$$

$$2\,pq = 0.18$$

$$p^2 = 0.01$$

And among the siblings of a hypertensive proband the proportion of hypertensives would be 0.58:

$$1 - \frac{pq^2(1 - p/4)}{1 - q^2} = 0.58$$

Platt's summary is highly quotable: "This paper re-examines the data of Hamilton, Pickering, Fraser Roberts, and Sowry on essential hypertension and gives reasons for doubting their hypothesis as to its nature. It is quite short. The reasons cannot be summarised and those who seek to understand the arguments should therefore read the paper."

As in Morris' studies of coronary artery disease, data from the drivers and conductors of London buses were used by Morrison and Morris. Although the curve for blood pressure in all cases was essentially continuous, that for those men one or both of whose parents had died in middle age was found to be bimodal (Fig. 13, *A*). This suggested the existence of two groups, one of which inherited the "dominant" gene and one of which did not. A reciprocal analysis involved the analysis of age of death in the fathers of hypertensive drivers. Here a distinct bimodality was demonstrated (Fig. 13, *B*) which suggested that some of the hypertensive drivers inherited the "dominant" gene from the father and some inherited

VOL. 12 196

it from the mother. The authors quoted the paper of Harris and Smith (1949) which analyzed the considerations determining whether bimodality is evident in a distribution curve: relative sizes of the two populations, the difference between the means, the standard deviations in the two populations, etc. Furthermore, they point out that the question of a unifactorial genetic factor in essential hypertension is of more than academic interest. A single genetic factor implies a single biochemical defect which can be sought and perhaps treated. (For example, a defect in O-methyl transferase, as suggested by Mendlowitz, Gitlow, and Naftchi, would be consistent.) Conversely, the polygenic theory of blood pressure determination leads to the conclusion that hypertension is not a distinct entity and that there is no single factor in its etiology which can be attacked.

Platt pointed out that longitudinal studies of at least 20 years will be helpful in determining a crucial point in the above argument: whether there are two types of persons, those who in middle age have a rise of blood pressure to ranges usually considered hypertensive and those whose blood pressure changes little with advancing years. Cruz-Coke presented "longitudinal data" bearing on this matter. In a study spanning 12 years he found the following: Patients who

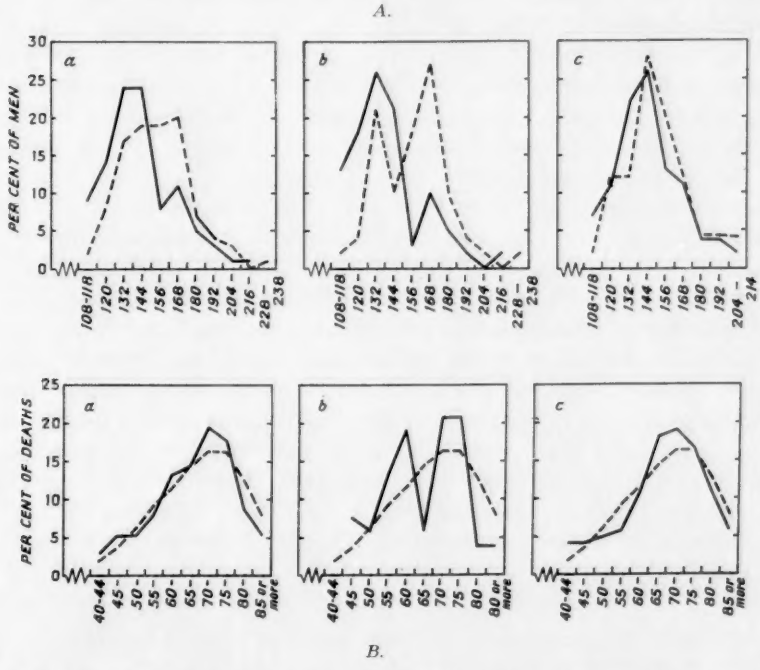


Fig. 13.—Biomodality with reference to essential hypertension. *A*, Distribution of casual systolic blood pressures in bus drivers aged 45 to 60 years: (*a*) all drivers (186 men); (*b*) drivers with one or both parents dead in middle age (90 men) (middle age = 40 to 64 years); (*c*) drivers with both parents living to old age (96 men) (old age = 65 years or over).

B, Distribution of ages at death (from all causes) of fathers of bus drivers aged 45 to 60 years. The interrupted line represents the distribution of ages at death of all men in England and Wales: (*a*) fathers of all drivers (174 deaths); (*b*) fathers of "hypertensive" (blood pressure 160/95 mm. Hg or over) drivers (53 deaths); (*c*) fathers of "normotensive" drivers (121 deaths). (From Morrison, S. L., and Morris, J. N.: Lancet 2:864, 1959.)

subsequently became hypertensive had, 12 years previously, mean diastolic pressures in the upper part of the "normal range" whereas those who remained normotensive had mean diastolic pressures in the lower part of the normal range. Similarly, the mean diastolic pressures of first degree relatives of hypertensive patients were high normal whereas those of normotensive persons were low normal.

Letters to the editor pointed out possible defects in the argument outlined above. Pickering suggested that the bimodality might be due to "unconscious digit preference," that is, the preference for recording blood pressure to the nearest 5 or 10 mm. He reiterated the reasons for accepting the polygenic nature of hypertension: (1) that it makes good biometric sense that level of blood pressure should be an algebraic summation of factors, (2) that the correlation of blood pressure in probands and first degree relatives holds at all levels of blood pressure in the proband, and (3) that the clinicopathologic effects of blood pressure elevation are quantitative. As a fourth point he stated that there are *not* two populations as to rate of rise of blood pressure. Without documentation he stated: "On this point the evidence is fairly conclusive."

Supporting the polygenic hypothesis, Keen and Rose suggested a different explanation for the bimodality observed by Morrison and Morris. Persons dying in middle age would constitute two groups: (1) those dying from various causes other than hypertension and (2) those dying from hypertension. Blood pressure in the sons of the first group would be expected to be distributed around the usual mode for the population. Blood pressure in the sons of the second group would be expected to be distributed around a higher mode. One would expect the composite curve to be bimodal.

Greenberg and Gardner reported an eighth family with multiple cases of pheochromocytoma. Father and son were affected. Furthermore, the interesting association between pheochromocytoma and von Recklinghausen's disease (neurofibromatosis) was again illustrated by the case of Chapman, Kemp, and Taliaferro. Davis and colleagues (1950) found that in at least 5 per cent of reported cases of pheochromocytoma stigmata of neurofibromatosis were described (Fig. 14). About 60 per cent of pheochromocytomas not associated with neurofibromatosis occur on the right side. Although it was previously thought that pheochromocytoma, when associated with neurofibromatosis, occurs predominantly on the left side (Healey and Makelatos, 1958), the later tabulation by Chapman and associates does not seem to bear this out. Café-au-lait spots and neurofibromas in a case of paroxysmal hypertension assist the diagnosis of pheochromocytoma.

508. Atherosclerosis, including coronary artery disease. McLeary and colleagues described 11 patients with xanthoma tuberosum of whom 6 had died. Five of the 6 had angina. In all, the skin changes developed before puberty. The family history was positive in 11. The patients had hypercholesterolemia without increase in neutral fat.

Albrink and Man concluded that elevated serum triglycerides are present in 85 to 90 per cent of cases of coronary artery disease and that this is a good measure of susceptibility to coronary artery disease.

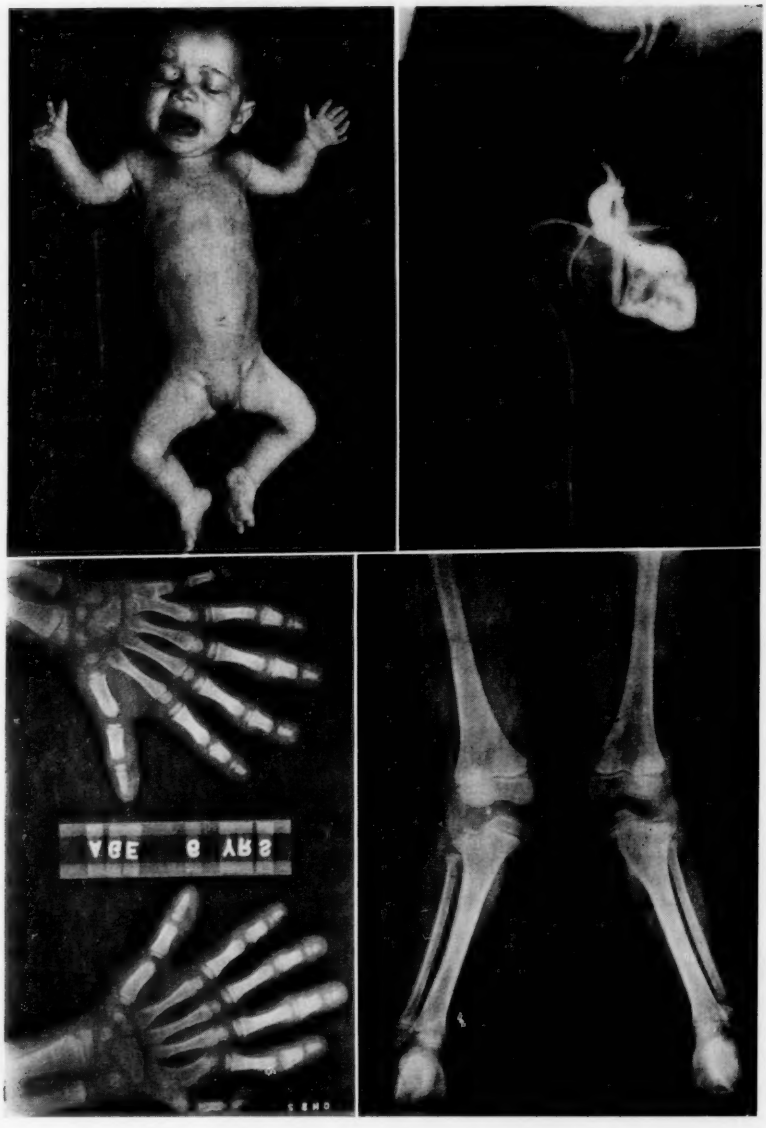
Kohn and Prozan suggest that hyperuricemia is as reliable an index of proneness to coronary heart disease as is hypercholesterolemia. Hyperuricemia appears to be associated with increased vascular disease, although better documentation is in order.

Fig. 14.—Pheochromocytoma in neurofibromatosis. Café-au-lait spots and neurofibromata in E. S. (J.H.H. 468773), from whom a pheochromocytoma was removed in 1950. Since that time the patient has remained normotensive or at the most mildly hypertensive.

Glotzer presented evidence that in Kings County Hospital, Brooklyn, myocardial infarction is much less frequent in the Negro than in the white person. Furthermore, he estimated that in the Negro the animal fat content of the diet is higher than the average for Brooklyn. He raised the possibility that differences in coronary arterial anatomy might account for differences in coronary atherosclerosis.

Several writers have attributed the immunity of the Bantu to coronary artery disease to a peculiarity (presumably genetic) of the gross anatomy of the coronary arterial tree as described by Brink (1949): "presence of a 'third primary division' of the left coronary artery and right coronary 'preponderance.' " Brink's experience was limited to 15 Bantu and 17 European hearts. Singer, in a study of 86 white persons, 83 Bantu, and 109 Cape Coloured, could demonstrate no differences in frequency of the several variants of coronary artery pattern.

A. B.



C. D.

Fig. 15.—The Ellis-van Creveld syndrome. *A*, Polydactyly and the short extremities are clearly evident in L. E. (B47024), a 4-month-old infant. The shortening of the extremities involves particularly the distal portions. *B*, A catheter introduced via a leg vein has passed into the left ventricle, presumably from a single atrium; the aorta and its branches are well demonstrated. *C*, The x-rays from another patient, C. H., aged 6 years, demonstrate in addition to polydactyly the characteristic fusion of the capitate and hamate bones of the wrist, as well as fusion of the fifth metacarpal with the anomalous one. *D*, The erosive change in the lateral portion of the proximal end of the tibia resulting in bilateral genu valgum is highly characteristic also.

In a group of Jewish men, Spain and Nathan could find no differences in urinary excretion of estrogens according to body type or to presence or absence of clinical evidence of coronary atherosclerosis. On the other hand, Tanner and colleagues did find a relationship between body build and urinary excretion of certain steroid hormones (¶531).

509. Rheumatic fever. Glynn, Glynn, and Holborow (1956) reported that there is an excess of nonsecretors among patients with rheumatic fever. The same workers, in 1959, presented more evidence for this (28.9 nonsecretors in patients with rheumatic fever as compared with 22.9 per cent in controls). The previous data were based on rabbit anti-Le^a precipitation studies of the Le^a substance present in the saliva of most nonsecretors. The new data were based on this test and also on "Ulex" tests. The authors suggest that all persons with rheumatic fever who are secretors are heterozygous (Se se). Essentially, they are suggesting that susceptibility to rheumatic fever is a dominant trait and not recessive as suggested by Wilson (1956 and before). Family studies will be necessary to establish this point. The authors suggested that the nonsecretion gene is a requirement for susceptibility to rheumatic fever. They calculated one could anticipate the incidence of rheumatic fever in the parents and siblings of patients with the disease to be not more than 13 and 16 per cent greater, respectively, than in the general population.

Addis determined ABO blood groups in 538 patients with rheumatic mitral valvular heart disease and in 5,898 consecutive new blood donors in the same area of Scotland. No significant differences were discovered.

510. Congenital malformations of the heart and great vessels. Discordance, with respect to ectopia cordis, in monozygotic twins (probable or proved) was described and discussed by Hurwitt and Lebendiger. In New York City, Ross collected information on 37 pairs of twins at least one of each of which had a congenital cardiovascular defect. Zygosity was determined by rigid criteria and data bearing on the nature of the malformation were collected. Two of 26 dizygotic twin pairs were concordant; 2 of 11 monozygotic twin pairs were concordant. One only of each of the remaining 33 pairs was affected.

Meredith and Clarkson reported the clinical findings as well as those of cardiac catheterization and autopsy in a 4-month-old beagle dog with tetralogy of Fallot. The features were identical to those in man. Availability of a group of such animals might assist in answering questions about the genetic background as well as physiologic questions.

Foxon discussed hereditary and other factors in congenital heart malformations. Mechanical factors related to blood flow are suggested as important in normal formation of septa. It was pointed out that in poultry persistent left aortic arch is gene determined. Campbell described forty families with 2 or more cases of congenital heart disease (total of 88 cases). It tended to be the same malformation in the acyanotic group and different in the cyanotic or mixed group. He points out that the empirical risk to further pregnancy is not great and should not carry any weight in family planning. In 2 pairs of twins (almost certainly

monozygotic) there was concordance for patent ductus arteriosus in one and for small ventricular septal defect in the second. Rowen described coarctation of the aorta in a 48-year-old father and his 21-year-old son.

Two siblings with the Ellis-van Creveld syndrome (dyschondroplasia, polydactyly, dysplasia of fingernails and teeth, and congenital heart disease) were described by Taylor, Schonholtz, and Geppert, and other cases from the literature were reviewed. Walls, Altman, and Winslow added a twenty-fifth case to the literature and pointed out that parental consanguinity was recorded in 9 of the 25. The most frequent form of cardiac malformation is cor triloculare monatriatum. (see Fig. 15).

Gorham and Merselis found the Kartagener syndrome (situs inversus viscerum, bronchiectasis, and malformation of the paranasal sinuses) in 2 of 5 siblings. A review of cases at the Johns Hopkins Hospital suggested rarity of the condition in Negroes. Case reports were provided by Streete and Stull. Hummel and Chapman studied *situs inversus viscerum* in mice and concluded that it is inherited as an autosomal recessive trait with incomplete penetrance.

VOL. 12 196(

Miscellaneous: 511. Bryant and Bozian suggested that in the normal heart there are four clear-cut *electrocardiographic phenotypes* based on the form of the QRS, which in turn is based on the sequence of ventricular activation. The genetic hypothesis advanced by the authors postulated two pairs of alleles, one determining sequence of septal activation and the other free-wall activation. They concluded that initial left septal activation is dominant to right and that late right free-wall activation is dominant to left. Evaluation of the hypothesis must await publication of family data. However, the fact that the relative proportion of the several phenotypes changes drastically during adult life makes it seem unlikely that the electrocardiogram will prove an easily analyzed genetic trait.

Harnischfeger described the Wolff-Parkinson-White syndrome in persons of three generations including a set of identical twins who were concordant and a set of fraternal twins who were discordant. Evidence was also presented to indicate that an accessory pathway between atrium and ventricle permits "re-entry" from the ventricle. In the study by Warner and McKusick (1958) of families of 16 patients with this syndrome, no secondary cases were discovered.

512. Bird and Jacques concluded that the primary vascular lesion in *hereditary hemorrhagic telangiectasia* (Fig. 16) is located in the veins. Pulmonary arteriovenous fistulas (Fig. 17) were discussed as a manifestation of this disease by Le Rout, by Sammons, and by Hodgson and coauthors. The latter group concluded that 39.4 per cent of 231 members of a large kindred had multiple telangiectasia and that of the affected persons 15.4 per cent had pulmonary arteriovenous fistulas. Conservative segmental resection is indicated because more fistulas, requiring further surgical operation, may appear later.

Stich thought that Adrenosem (carbazochrome salicylate), administered intramuscularly and orally, is effective in controlling bleeding in Osler-Rendu-Weber disease. Adrenosem is a synthetic epinephrine-like material which is

said to have a specific effect on capillaries: to increase their tone and reduce their permeability.

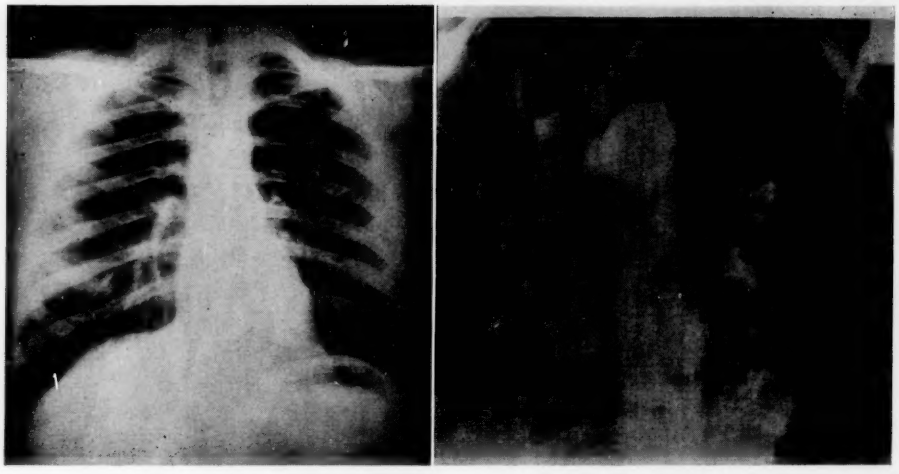
513. Di Sant'Agnese reported further on a family with *cardiac glycogen storage disease* apparently inherited as an autosomal recessive trait.

Coleman, Edmunds, and Tregillus described a brother and 2 sisters with *primary pulmonary hypertension.*

Fig. 16.—Mucosal lesions of Osler-Rendu-Weber hereditary telangiectasia. R. L. (J.H.H. 612189), 50 years old, has had chronic gastrointestinal bleeding.

514. Faivre, Gilgenkrantz, and Panther described a family in which 2 brothers aged 20 and 14 and a sister aged 26 had idiopathic cardiomegaly with changes of left ventricular hypertrophy and "strain" by electrocardiogram. The 26-year-old and an unaffected sister each had a son with isolated, unexplained cardiomegaly. Schiebler, Adams, and Anderson described a 13-year-old girl and her 16-year-old brother who had *familial cardiomegaly* with the Wolff-Parkinson-White syndrome. The association has been reported several times before. An 18-year-old brother is normal, as are also the parents. Garrett, May, and Rickards described familial cardiomegaly in the 3 youngest of 6 siblings. All 3 died suddenly after apparent good health up to the day of death—2 at age 18, one at age 30. Necropsy details were available in one case: marked hypertrophy of left ventricle with macroscopic and microscopic fibrosis. Voridis and Maurice described other families with multiple members affected by familial cardiomegaly.

Thorén described a family in which there were three consanguineous marriages. Each of two of these marriages resulted in 2 cases of Friedreich's ataxia with combined neurological and myocardial disease. Myocardial disease only was present in 2 members (aged 14 and 32 years). Progression, then regression, of electrocardiographic changes were noted. Serum transaminase and lactic acid dehydrogenase levels were not elevated on repeated determinations during periods of seeming activity of the disease as indicated by electrocardiogram. The author states, "In all likelihood only one gene is defective in the purely nervous disease. The combination, which is reported in 30 per cent, would need another defective



A. *B.*

Fig. 17*A* and 17*B*.—Pulmonary arteriovenous fistulae in Osler-Rendu-Weber hereditary telangiectasia. M. R. M. (J.H.H. 663074), a white male college student born in 1932, was admitted to the hospital in 1954 because of cyanosis. About 10 months before admission he had had an episode of numbness of the ulnar side of the left hand progressing up the arm, with incoordination of the arm followed in a few days by the onset of occipital headache, vomiting, and fever. Stiff neck and pleocytosis of the spinal fluid were discovered. Treatment with penicillin and a sulfonamide was given with apparent success and the patient was well until 3 months before admission when, while climbing stairs to the balcony of a theater, he became dyspneic, developed the same type of occipital headache, and lost consciousness for several minutes. Severe vomiting followed recovery of consciousness. Apparently he completely recovered in a few days.

On examination the patient demonstrated telangiectases of the mucous membranes, cyanosis of the nail beds with slight digital clubbing, slight papilledema, and a blowing murmur at the left lung base just to the left of the spine. *A*, X-rays of the chest showed only suspicious increase in the lung markings in the left lower lobe behind the heart. *B*, Angiocardiogram revealed unusually early filling of the left atrium. There was an extensive arteriovenous fistula which appeared to be limited to the left lower lobe. Cerebral arteriogram showed a space-occupying lesion of the right temporal lobe. The hematocrit was 56 per cent.

gene. Moreover, the latter defect might just as well occur by itself." A single pleiotropic gene expressed mainly in the homozygous state would seem more likely to the reviewers. Thorén's pedigree is consistent with the possibility that the persons with only the myocardial disease are heterozygotes.

515. McKee and Edgerton described a reconstructive operation for lymphedema of the legs which would presumably be applicable in *Milroy's disease.* Warwick and colleagues reported the fifth case of a syndrome consisting of chylous ascites and lymphedema of one or more extremities. The lymphedema can involve only an arm and can be unilateral. Both lymphatic channels and lymph nodes are ill-formed. The lymphocytes are low in count in the peripheral blood. There is no evidence of heritability. Mention is made here only by way of comparison with Milroy's hereditary lymphedema. Involvement indistinguishable from Milroy's disease occurs relatively frequently in sporadic cases; the minority of cases (less than 20 per cent) show a positive family history.

VOL. 12 1960

C. *D.*

Fig. 17*C* and 17*D*.—Craniotomy was performed and there was discovered a cyst of the right temporal area which was excised. About 2 months later left lower lobectomy was performed. *C*, The appearance in situ of the left lower lobe. *D*, an x-ray of the injected specimen.

It is of note that the typical telangiectases on the mucosal surface of the lips were discovered only when the possibility of Osler-Rendu-Weber disease was raised during discussion of the patient at Grand Rounds—this in spite of a hospital stay of 4 months' duration and examination by representatives of many services.

516. Genecin described *chronic pericardial effusion* in 2 brothers; in one the picture was that of "cholesterol pericarditis." There is, of course, no certainty that a genetic factor was involved, rather than, say, an infectious element. In a sibship with multiple cases of "familial myocardopathy" we have observed chronic pericardial effusion as a leading feature; here, too, an infectious agent may be responsible for the "familial aggregation." Pericardial effusion probably occurs as an aspect of the cardiac involvement of Freidreich's ataxia.

517. Van Buchem, Arends, and Schröder described *endocardial fibroelastosis* in 5 adolescents and adults, aged 13, 16, 18, 26, and 46 years at death. They suggest that this is the same disease as causes death in the first years of life. If true, a new aspect which must be considered in family studies has been added. (See the discussions of Lehndorff.)

XII. CONNECTIVE TISSUE

518. The Marfan syndrome. Case reports were provided by Gleditsch, by Reid, by Ferguson and Clemente, by Diu and Agarwai, and by Gordon, among others. In an elaborate review, Versé discussed all aspects of the Marfan syndrome in a comprehensive manner.

In rabbits, Schwartz found that experimental lathyrism (which has features, especially aortic and skeletal, resembling those in the Marfan syndrome) is

characterized by separation of the elastic fibers of the aortic media, increase in metachromatically staining material, and increase in serum hexosamine and mucopolysaccharide.

The action of chymotrypsin in dissolving the zonular fibers of the lens—discovered serendipitously by Barraquer in Spain and developed by him as an adjunct in lens extraction for cataract (Henderson)—is of interest in connection with the nature of the zonular fibers. It has been suggested that if it were known what the aortic media and the suspensory ligament of the lens have in common, one might be closer to understanding the basic defect in the Marfan syndrome.

Miller and Pearson described a 27-year-old Negro woman with classic Marfan syndrome in whom aortic stenosis was simulated by mitral regurgitation: at autopsy a "jet lesion" was found on the wall of the left atrium opposite the mitral orifice. The authors suggested that the regurgitant stream impinged on the aortic root and because of its peculiar radiation the murmur simulated one arising from the aortic valve itself. An unusual feature was the demonstration of extensive calcification in the mitral annulus fibrosis and valve cusps. A giant left atrium was present. Although there can be little doubt of the diagnosis of Marfan syndrome—the skeletal features were striking and ectopia lentis was present—the aorta showed no cystic change. The mitral valve disease appears to have been due to rheumatic fever and complicating bacterial endocarditis. There is no evidence for more than a coincidental association of the Marfan syndrome and rheumatic fever.

VOL. 12 1960

Wever, Edwards, and Brandenburg described a 53-year-old man with aortic regurgitation secondary to dilatation of the ascending aorta. Skeletal and ocular abnormalities were lacking and, except for some cases of varicose veins and of unexplained heart disease, the family history was negative. Nevertheless, the authors suggested that this was a case of the Marfan syndrome because the gross and histologic changes were so typical and because they questioned that the alternative possibility, idiopathic cystic medial necrosis, produces sacculation of the aortic cusps and medial changes in the pulmonary artery such as were found in this case.

An impressive feature of the aortic involvement in the Marfan syndrome is the predominance of changes in the ascending aorta. A concentration there of certain hemodynamic stresses, particularly expansile pulsation, may be responsible for the localization of most striking changes in this part. Occasionally, however, abdominal aneurysm occurs without clinical signs relating to the thoracic aorta. Hardin described such a case.

Van Buchem studied a 21-year-old man with the Marfam syndrome. Ectopia lentis and dolichostenomelia were present. The mother and one brother were also affected. Clinically, a loud systolic murmur with protodiastolic gallop, left bundle branch block, and cardiomegaly were present. Autopsy revealed marked hypertrophy and dilatation of both atria and both ventricles, relative insufficiency of the mitral and tricuspid valves, and moderate fibrosis of the myocardium without valvular defects. It is difficult to account for these findings on the basis of a generalized defect of connective tissue, or, at least, to reconcile them with other autopsy experience in the Marfan syndrome. Mitral regurgitation as the predominant or only cardiac lesion is sometimes found, but usually in such cases

multicuspic malformation and redundancy of the chordae tendineae have been found to account for the clinical picture.

Golden and Lakin described, as a "forme fruste" of the Marfan syndrome, 4 members of the same family with pterygium colli. Three of the 4 were suspected to have atrial septal defect. There was no ectopia lentis and height was below average. We find it impossible to see what evidence there is for the diagnosis of the Marfan syndrome. "Any old" skeletal change in association with suspected congenital malformation of the heart does not lead to the diagnosis of the Marfan syndrome. On the other hand, in the pterygium colli syndrome of Bonnevie-Ullrich, cardiovascular malformations are known sometimes to occur.

Mitoma and associates described their improved method for measuring hydroxyproline. Their preliminary data suggesting increased urinary excretion of hydroxyproline in the Marfan syndrome (see ¶178) and normal excretion in the Ehlers-Danlos syndrome were included.

Tuna described a venous aneurysm in the right supraclavicular fossa in a 42-year-old man thought to have the Marfan syndrome. The diagnosis seems to have been based on the presence of a habitus suggesting the Marfan syndrome and mitral regurgitation with cardiac failure. However, impotence, small testes, and absent spermatogenic cells on testicular biopsy are more suggestive of the Klinefelter syndrome, which causes a Marfanoid habitus (see ¶553).

Everberg found a high-tone hearing loss in an 11-year-old girl with the Marfan syndrome. He suggested it was a nerve type of deafness. Deafness in the Marfan syndrome has been previously noted but has not been systematically studied and its mechanism is not understood.

Bowers, in a family with many members affected by the Marfan syndrome, described 2 in whom the diagnosis of the Weil-Marchesani syndrome (short stature, brachydactyly, brachycephaly, and ectopia lentis) seemed justified to him. He concluded there is a genetic relationship between the two syndromes. One of the cases which he labeled Weil-Marchesani syndrome was in the youngest affected individual of his study, aged 3 years. The habitus in the Marfan syndrome is often difficult to evaluate at this age. The second case, indeed of short stature, was not studied at first hand. Thus, the evidence for his thesis is flimsy. Bowers emphasized the occurrence of a high-pitched voice of unusual timbre as a feature of the Marfan syndrome.

Kravitz made a plea for early surgical operation on the lens (discission). He doubted that there is increased risk of inducing either detachment of the retina or glaucoma.

519. The Ehlers-Danlos syndrome. The group in Leeds (Tunbridge, 1956) reported that serum elastase inhibitor was elevated in 2 cases of the Ehlers-Danlos syndrome. Walford and Schneider reported studies of the inhibitor in man and animals. Values in women are somewhat higher than those in men and in the third trimester of pregnancy very high levels occur. No consistent pattern was found in systemic lupus erythematosus, dermatomyositis, arteriosclerosis, liver damage, and the nephrotic syndrome. The Ehlers-Danlos syndrome was not studied.

Boileau and Dionne described a woman with this syndrome who in the seventh month of pregnancy suffered from severe pain in the pelvic joints. The pain was so severe as to prevent her walking. An infant weighing 3 pounds was delivered by cesarean section, but it lived only 8 hours and at autopsy showed a congenital malformation of the heart (details not given).

In a case of presumed Ehlers-Danlos syndrome reported by McFarlane the presenting manifestation was thoracolumbar kyphoscoliosis with wedge-shaped deformity of vertebral bodies. Zaidi described a full-blown case of the syndrome in a 3-year-old French Canadian boy in whom pigeon breast and congenital umbilical and inguinal hernias were present.

520. Osteogenesis imperfecta. Osteogenesis imperfecta without blue sclerae or deafness was observed in three generations of a family (Bryan and di Michele) (see ¶400).

Laplane and his colleagues discussed the question of whether osteogenesis imperfecta congenita is the same disease as osteogenesis imperfecta tarda and tried to make the case that the former is a recessive trait separate from the dominant latter form. They refer to the congenital form as "periosteal dysplasia of Porak and Durante" (this designation has been used mainly in France) and to the late form as "osteopsathyrosis." They review reports from the literature of the two forms in the same family. Furthermore, they found three reports of the congenital form occurring in an isolated offspring of a consanguineous mating. They refer to 2 sibships which were offspring of consanguineous marriages and in each of which 2 children were affected. The pedigree they reported contained 19 patients with periosteal dysplasia of which 15 were born of consanguineous matings. The pattern in this large pedigree is consistent with recessive inheritance. Unfortunately, no clinical data, no comment on the sclerae, and no x-rays are provided; therefore, an independent judgment on the phenotypic nature of the disease in this family is not possible. Clement defended the identity of the congenital and the "tarda" forms.

McCaslin and Janes reported on the use of strontium lactate in the treatment of acquired osteoporosis. It should be tried in the hereditary osteoporosis of osteogenesis imperfecta.

Stool, Sullivan, and Bigelow underscored the wide range of expressivity of osteogenesis imperfecta by describing a 95-year-old white female with blue sclerae, loosejointedness, multiple fractures, and impaired hearing in a family with multiple cases.

521. Pseudoxanthoma elasticum. Coffman and Sommers described a woman with pseudoxanthoma elasticum who died of congestive heart failure due to tight mitral stenosis. The authors thought the mitral stenosis was an integral part of the disease. The husband was unaffected; 5 of the 6 children had pseudoxanthoma elasticum of the skin by clinical examination and biopsy and had cardiac murmurs and cardiomegaly. Dominant inheritance was suggested. Although a few pedigrees are consistent with dominant inheritance, pseudoxanthoma elasticum has been thought to be usually an autosomal recessive characteristic.

Putkonen and Wangel described metastatic calcification of the skin in a case of congenital renal dysplasia and commented on the fact that "at first glance [the skin lesions] resembled pseudoxanthoma elasticum to some extent." We have observed a patient with similar manifestations.

Paton described angioid streaks, apparently indistinguishable from those of this disease, in cases of sickle cell anemia. Also, in passing, he referred to a new case of pseudoxanthoma elasticum skin changes, angioid streaks, and Paget's disease of bone; 3 such cases have been previously described in the literature.

Robertson and Schroder described 3 cases of pseudoxanthoma elasticum. In 2 of the 3 patients migratory polyarthritis was described. Arthritis has not been a prominent feature in previously described cases. In one of the 3 the diagnosis of this disease seemed well grounded. The patient also had arachnodactyly and was labeled as having the Marfan syndrome. The skeletal features of the Marfan syndrome are sufficiently nonspecific to make them a dubious basis for any useful conclusions about a relationship between pseudoxanthoma elasticum and the Marfan syndrome.

Cases were reported by Levy and Brewer and by Wilkins and Sommers.

Carlborg and colleagues, including Ester Grönblad, whose name with Strandberg's is sometimes attached eponymically to this syndrome, reported clinical, hemodynamic, arteriographic, ophthalmologic, and pathologic studies of 29 cases of pseudoxanthoma elasticum, the largest series of cases collected to date. Claudication occurred in 13, angina of effort in 15, and psychiatric disorders of some degree in 24. Autopsy revealed changes in the endocardium of the left atrium and in the blood vessels of the stomach.

522. The Hurler syndrome. A sixth case of gargoylism in a Chinese child was described by Chou Yi-Che.

Steen described what he called Hunter's polydystrophy, the sex-linked recessive form of gargoylism. In 3 males of one sibship there were striking cardiac signs but normal mentality and certainly not the typically ugly face. The author stated that the diagnosis is made by the characteristic deformity of face, chest, and extremities, by the x-ray changes (in the spine, especially), and by corneal opacities. In fact, the sex-lined recessive type of gargoylism probably never shows corneal opacification—a phenotypic distinction from the autosomal recessive form of the disease. Two of the 3 children had both systolic and diastolic murmurs; one had a systolic murmur at the apex and at the base.

Murray described 2 patients with the Hurler syndrome and marked respiratory disability. One case was that of a child affected almost certainly by the autosomal recessive form of the disease because the corneas were hazy and death occurred at an early age. The second case probably represents the sex-linked recessive form of the disease, since the corneas were not clouded and the patient was living at a relatively advanced age with little impairment of intellect (Fig. 18). Although there can be no serious question of the diagnosis, the man displayed somewhat unusual features. He was 43 years old and had had at least enough intelligence to do defense work during World War II and to work as a flagman on construction jobs thereafter. Dwarfism, limitation of joint mobility, deafness,

somewhat grotesque facies, short neck, kyphoscoliosis with mild pectus excavatum, hernias, hepatosplenomegaly, and pallor of the optic discs with visua, impairment were all characteristic features in this man. Deformity of the larynxl nasopharynx, and tongue seemed to be responsible for airway obstruction. This view was supported by the marked relief afforded by tracheostomy. The patient had had a functioning tracheostomy for over 10 years. Kyphoscoliosis, restriction of chest movement, upper airway obstruction, chronic respiratory infection, and abnormalities of diffusion from parenchymal involvement by the basic process are mechanisms in the respiratory disability.

Fig. 18.—Probable sex-linked recessive variety of Hurler's syndrome in a 43-year-old man. (Courtesy of Dr. John F. Murray, Los Angeles.)

Kobayashi demonstrated granules of acid mucopolysaccharide in the epithelial cells of the glomeruli of 3 patients with the Hurler syndrome. The relation to the hypermucopolysaccharidurla and the Reilly bodies of the leukocytes was discussed. He suggested that liver or spleen biopsy might be useful in the mild sex-linked form when the diagnosis is in doubt. However, as far as now known, all such patients excrete excessive amounts of mucopolysaccharide in the urine; hence, the urine test is the preferable method of diagnosis. Heremans, Vaerman, and Heremans described an electrophoretic method for separation of acid mucopolysaccharides in normal urine.

Meyer and colleagues reported further studies of mucopolysaccharides. In 9 cases, all had chondroitin sulfate B as the major component of the urine and heparatin sulfate as a minor component. In the one patient studied a decrease in urinary excretion occurred with administration of prednisone. The same two

mucopolysaccharides were found in the organs of 5 patients on autopsy. In 3 the mucopolysaccharide in the liver was about 90 per cent heparitin sulfate; in one the two mucopolysaccharides were present in about equal amounts. Two brains showed both mucopolysaccharides. In one of these about 85 per cent of the mucopolysaccharide was chondroitin sulfate B. In normal brain no chondroitin sulfate was identified.

Engfeldt, Hulth, and Westerborn studied the effects of papain on cartilage. Essentially, a chondrodystrophy is produced and acid mucopolysaccharides appear in excess in the blood and urine. This work is of interest as a possible experimental model of the Hurler syndrome, just as lathyrism bears similarities to the Marfan syndrome. In both cases the similarity may be only superficial, however.

Others: 523. Léri's pleonosteosis may be a generalized hereditary disorder of connective tissue. Few cases have been reported in the British literature and probably none in the American literature prior to the report of Rukavina and associates of Ann Arbor. These authors described the disease in members of four generations of a Caucasian family. Presumably, the same family was referred to by Neel and Schull *Human Heredity*, 1954, p. 309. The features are short stature, Mongoloid facies, short spadelike hands, broad thumbs in valgus position, genu recurvatum, and generalized limitation of joint mobility. The gait is characteristically shuffling and short stepped. Thickening of the palmar and forearm fascias can be detected clinically. The most striking radiologic abnormality was enlargement of the posterior neural arches of the cervical vertebrae. Autosomal dominant inheritance was suggested.

Osteopoikilosis ("spotted bones", osteopathia condensans disseminata, osteodermatopoikilosis) was described by Melnick in 17 certain and 3 possible instances of four generations of a family. In the first generation studied both parents were affected although purportedly unrelated. The frequency of the condition is about one in 20,000. All of their 8 children were affected. Assuming autosomal dominance for the trait, the probability of all 8 being affected is $(\frac{3}{4})^8$, or about 10 per cent. Severely affected persons may be homozygous for the mutant gene; there were 4 such individuals but only one had all definitely affected children. This trait and this family might be usable for linkage study.

524. Boyd and Grant presented the autopsy findings in a 62-year-old man with *the Werner syndrome* (¶188). The rambling and loosely written report is confused from several points of view including the genetics; the authors state that the Werner syndrome is "probably an inherited heterozygous recessive character."

525. In Scotland Bremner, Alexander, and Duthie studied 202 first-degree relatives of 63 patients with *rheumatoid arthritis*, in whom the sensitized sheep cell test had been consistently positive or consistently negative. Clinical, radiologic, or serologic evidence of rheumatoid arthritis was found in 7.6 per cent of the relatives of patients with positive tests and in 6.4 per cent of relatives of those

with negative tests. As the authors stated, "it is impossible at present to offer a satisfactory explanation for the difference between the results of this investigation and that of Lawrence and Ball," who in a study in Leigh in Lancashire found much more serologic, clinical, and radiographic evidence of rheumatoid arthritis in the relatives of sero-positive probands than in relatives of sero-negative probands. It was noted that in Lancashire the frequency of sero-positivity was higher than that of signs of clinical disease, whereas the opposite was true in Scotland.

Malawista, Boies, and Seides found no clinical evidence of rheumatoid arthritis in natives of Liberia.

For a discussion of the relationship of rheumatoid arthritis to the Gm serum types, see ¶'s 320 *n* and 254.

526. O'Connell studied the parents and siblings of 87 cases of *ankylosing spondylitis* and found 16 certain or very probable cases of spondylitis and 7 of rheumatoid arthritis. He concluded with earlier workers that autosomal dominance with penetrance varying according to sex explains the inheritance. He, like others, observed the curious increase in familial incidence when the proband is female. Bugel and Alsobrook saw Marie-Strumpell spondylitis in both of male identical twins. Onset was at 18 years in one and 21 years in the other.

527. Kunkel remarked on the apparently increased frequency of rheumatoid arthritis and of positive serologic tests for rheumatoid arthritis in the families of probands with *systemic lupus erythematosus*. In one family 6 siblings developed rheumatoid arthritis and the time of onset of the disease is different siblings was as far as 40 years apart. He presented the pedigree of a child with classic juvenile rheumatoid arthritis whose mother and grandmother, although asymptomatic, had positive serologic tests. In some families positive serologic tests have been observed in the paternal branch, thereby rendering direct, nongenetic transmission from mother to offspring less likely. In four families of probands with acquired agammaglobulinemia, one or both parents showed positive serologic tests for rheumatoid arthritis. In two additional families lupus erythematosus was found in relatives of the patients with agammaglobulinemia. As was first pointed out by Janeway and his associates (1956), an arthritis resembling rheumatoid arthritis and lupus erythematosus occurs in a high proportion of patients with agammaglobulinemia.

Beckett and Lewis observed a 32-year-old woman with discoid lupus erythematosus and her 61-year-old mother with L.E. cells, cirrhosis, and a history of joint and pleural involvement.

Larsson and Leonhardt discussed hereditary hypergammaglobulinemia (HGG) and systemic lupus erythematosus (SLE). SLE occurred in 3 of 14 siblings. One other had marked HGG and 3 others had moderate HGG. A further 102 relatives in this pedigree were studied. In a second family 2 cases of SLE and one of rheumatoid arthritis were found among 5 siblings. One of the SLE patients was an identical twin; the co-twin had HGG. A distant female relative probably had SLE and several other members of the kindred had HGG. In a total experience of 43 families (both parents and at least one child), a correlation

VOL. 12 196

($r = 0.50$) was found between the γ globulin of fathers and children, none between other combinations. The authors present evidence that several of the cases of SLE developed against a background of chronic HGG. Several patients who subsequently developed manifestations of SLE had chronically elevated sedimentation rates. The hypothesis advanced by the authors was that SLE and rheumatoid arthritis may be related entities and that a genetically determined tendency to overproduction of γ globulins may be involved in their pathogenesis. "The disease symptoms may be ascribed to the development of autoantibodies."

Leonhardt did serologic studies in these same families using persons married to members of the pedigree as controls. An unexpectedly high frequency of positive antistreptolysin titers was found. Several other serologic peculiarities were found in probands and their close relatives.

Although perhaps not of direct genetic significance, the behavior of the L.E. factor is of tangential interest. The serum factor, a γ globulin, circulating in the blood of patients with systemic lupus erythematosus can, by standard serologic techniques, be demonstrated to react like an antibody with desoxyribonucleoprotein. Both DNA and histone are necessary to the reaction. Holman and Deicher analyzed the reactions in considerable detail. "The pathogenic significance of the antinuclear factors is unknown. Considerable evidence suggests that these factors cannot enter a normal cell *in vivo*. They therefore appear to be byproducts of an abnormal immune system rather than responsible pathogenic agents. However, exploration of this question is in its infancy."

OL.
12
960

XIII. EAR

528. The data of Stevenson and Cheeseman (¶189) on congenital deafmutism in Northern Ireland continued to stimulate much interest. Chung, Robison, and Morton applied what they term "more precise genetic methods" to the data and conclude that some of the earlier conclusions are supported, others not.

Arnvig described 4 unrelated individuals with *the Waardenburg syndrome* (Fig. 19). In 3 the pedigree pattern was consistent with a dominant trait with variable expressivity: the deafness was unilateral in some; only heterochromia iridis was present in some. The fourth was interpreted as a possible mutation; however, abnormality of pigmentation (type not specified) was present in 3 collateral relatives. The author disputed Waardenburg's view that the syndrome is the polyphenous* result of a single dominant gene. Instead he held that most aspects of the syndrome are inherited dominantly whereas the deafness is recessive. A hypothesis of gene-linkage is, therefore, proposed. Gene-linkage is theoretically an unacceptable explanation of multifaceted hereditary syndromes. However, it may be true that the monogenic hypothesis is something of an oversimplication. Certainly we need to know much more about the reason for variable and incomplete expression of the several manifestations in such syndromes. Partington described the pedigree of an affected English family and defended

*Although it has been rarely used, "polyphenous" (or "polyphenic") seems a good term to describe the behavior of a gene with various and manifold manifestations.

Fig. 19*A*.—Waardenburg's syndrome. L. H. (738013), aged 5 years, has congenital nerve deafness, wide bridge of the nose, partially white eye lashes, white forelock, and a history of operation for Hirschsprung's disease at the age of 2 years.

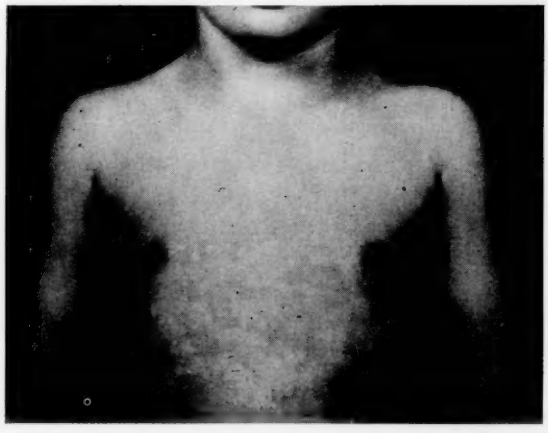


Fig. 19*B*.—There were also areas of leukoderma elsewhere on the body, such as over the anterior chest.

VOL. 12 196

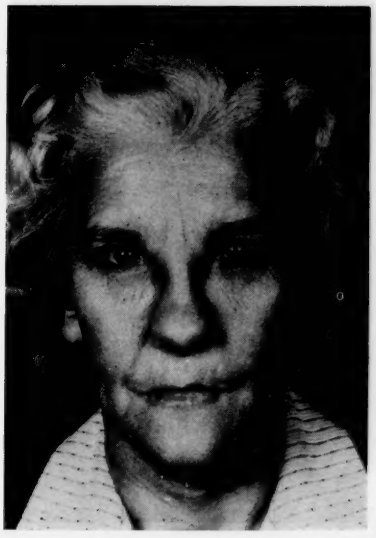


Fig. 19*C*.—The paternal grandmother had premature graying of the hair (by the age of 30 years) and has a very wide nasal bridge but no deafness.

Fig. 19*D*.—The paternal grandmother also has several areas of depigmentation, such as over the shins. Several of her close relatives have Waardenburg's syndrome in various degrees of severity or completeness. The father of the proband has not been studied; however, he is said to have "slight eye folds" and he had a white forelock at birth which disappeared when he was 3 or 4 months old.

simple autosomal dominant inheritance. Fisch reported on 35 cases of the Waardenburg syndrome. Low tones tended to be more involved in the hearing loss than high tones. Histologic examination in one patient who died of bronchopneumonia showed in the cochlea absence of the organ of Corti and marked reduction in the number of nerve fibers in the spinal canal. Esophageal atresia occurred in some subjects with this syndrome.

Rainer and Firschein gave a preliminary report on a study of persons deaf from birth or early childhood. A high marriage rate was found and the rate was especially high for those deaf persons both of whose parents had been deaf. About 94 per cent of the sample were the offspring of 2 hearing parents. In over 27 per cent of marriages where both partners were born deaf and from about 12 to 15 per cent of those where one partner was born deaf resulted in at least one deaf child.

Lang described retinal degeneration and nerve deafness in 5 of 10 offspring from a marriage of first cousins. The mother had retinal degeneration only; the father was not examined.

VOL. 12 196

XIV. ENDOCRINE SYSTEM

529. A general review of genetic aspects of pediatric endocrinology was provided by Gardner, Rosenthal, and Feinberg. Hypopituitarism, pheochromocytoma, familial goitrous cretinism, intersex states, and virilizing adrenal hyperplasia were discussed. A serologic method for insulin assay was described.

Adrenal: 530. Schneeberg and colleagues described *virilizing adrenal hyperplasia* in a set of identical twins. Although the genetic basis of the syndrome and simple autosomal recessive inheritance are well established (Childs, 1956), this is only the second reported twin pair.

Gans and Ser described the first case of normal pregnancy and delivery in a patient with adrenal hyperplasia, after she had been on cortisone for 4½ years.

In 1956 Gardner described a patient with congenital adrenal hyperplasia and periodic fever. The demonstration by Bondy (1958) that plasma etiocholanolone is increased during periods of fever in cases of idiopathic periodic fever led to reinvestigation of the case (Gardner and Migeon), with the conclusion that a similiar elevation may be present in the patient with congenital adrenal hyperplasia.

Elsewhere Gardner, Rosenthal, and Feinberg suggested that there are five types of congenital adrenal hyperplasia:

a. Simple virilizing
b. Virilizing plus salt losing
c. Virilizing plus hypoglycemia
d. Virilizing plus hypertension
e. Virilizing plus periodic fever

Jailer, Ulick, and Lieberman described cases of the salt-losing form of congenital adrenal hyperplasia in which aldosterone secretion and hydrocortisone

secretion were normal. Mineralocorticoids, in about twice the dose required by an Addisonian patient, maintained one patient in electrolyte balance. Administration of ACTH caused a marked increase in urinary sodium. The authors suggested that these patients secrete a distinctive but as yet unidentified substance which increases sodium excretion or antagonizes the effect of aldosterone. Unlike aldosterone, the anomalous substance appears to be under ACTH control.

531. In 2 brothers Mitchell and Rhaney diagnosed *congenital adrenal hypoplasia.* One died in adrenal insufficiency at the age of 2 months; with therapy the other had survived to 11½ months. Hypoparathyroidism and moniliasis, features of other reported cases, were apparently not present. Shepard, Landing, and Mason described 2 sisters with idiopathic *Addison's disease.*

532. Tanner and colleagues correlated body build and urinary excretion of steroids in 101 male medical students. The week-to-week constancy coefficients were 0.83 for 17-ketosteroids, 0.73 for 17-ketogenic steroids, and 0.72 for creatinine. Excretion of 17-ketosteroids was significantly correlated with body weight and mesomorphy. The multiple correlation with muscle width and weight was 0.56. Excretion of 17-ketogenic steroids showed a multiple correlation of 0.55 with width and length of the limb bones.

See ¶507 for a discussion of the familial occurrence of pheochromocytoma and its occurrence in neurofibromatosis and von Hippel-Lindau's disease.

533. Meier and Yerganian have studied spontaneous hereditary *diabetes mellitus* in the Chinese hamster (*Cricetulus griseus*). The disease promises to be valuable for the study of the basic defect and inheritance and for screening of hypoglycemic agents. (The Chinese hamster has proved, in Yerganian's hands, very useful for chromosome studies. The chromosome number is one of the smallest known in a mammal [2n = 22] and the chromosomes are relatively large [Ford and Yerganian, 1958].) Genetic studies are to be reported later. Marked polyuria, glycosuria, blindness from cataract or corneal opacity, hydronephrosis, quantitative and qualitative changes in the β cells of the pacreas, and deposits of PAS-positive material in the renal glomeruli were described. Cardiovascular changes were conspicuous by their absence.

Diabetics do not differ from controls in the proportion of PTC tasters and nontasters (Åkerson).

Thyroid: 534. McGirr and his colleagues described goiter with euthyroidism and deaf-mutism in 5 persons, including 2 sisters and a brother and sister. Closely linked genes were thought to be responsible for the association of deafness and thyroid disease. Although linkage is possible, more likely is the presence of a single pseudopleiotropic, polyphenic (see previous footnote) gene. In a later paper the same authors indicated that the defect concerns the dehalogenase activity necessary to deiodinate monoiodotyrosine. In 4 apparently healthy members of a family they demonstrated the same defect in lesser degree; they concluded these may be heterozygotes.

McGirr, Hutchison, and Clement described impaired dehalogenase activity in the thyroid of an 11-year-old euthyroid girl in whom goiter had been present for 3½ years. The thyroid gland was multinodular and showed the changes of papillary adenocarcinoma in some areas. The mother showed evidences of a similar enzyme defect and a maternal aunt had had thyroidectomy for goiter. The sequence of events was thought to be as follows: impaired dehalogenase activity, compensatory thyroid hyperplasia, goiter, and neoplasia.

Carr, Beierwaltes, and Clure found a defect in organic binding of iodine in the euthyroid mothers of patients with familial cretinism.

De Groot and Stanbury described 5 cases of congenital goitrous hypothyroidism due, they thought, to a genetic defect. However, no direct evidence of a hereditary basis was available. Characteristic of these cases was the presence in the serum and the urine of an abnormal iodinated polypeptide or protein which was not extracted by butanol. There was increased uptake of I^{131} by the thyroid but no release of I^{131} by potassium thiocyanate. Deiodinase activity was normal.

Beierwaltes and colleagues also reviewed the methods for early detection of congenital hypothyroidism. The classic features, such as protruding tongue, potbelly, and obvious mental retardation, may not be recognizable until the age of 3 to 6 months, when it is too late to obtain optimum results from replacement therapy. The serum alkaline phosphatase activity is low in the infant with this disorder, as is also the protein-bound iodine. Umbilical hernia, prolonged cyanosis, and birth weight over 4,000 Gm. are features suggesting congenital hypothyroidism. Retarded growth, constipation, lethargy, anemia, dry skin, hypothermia, and bradycardia should be watched for. The authors described a woman who had borne 2 cretinous offspring. She was given thyroid during a third pregnancy. At 5 days of age the third infant was found to have a low level of protein-bound iodine. Development was perfectly normal with administered thyroid hormone. (The question might be raised as to whether the infant was in fact normal and its own thyroid had been suppressed temporarily by the thyroid hormone administered to the mother.) The authors stated that studies of serum levels of thyroid hormone in a severe endemic goiter area in India suggest that temporary congenital hypothyroidism may be a commoner cause of mental deficiency and deafness than is supposed.

Beierwaltes and Robbins described a man who, together with one of his 3 children, showed elevated protein-bound iodine and butanol-extractable iodine but functionally a euthyroid state. The basis of the paradox seemed to be increased thyroxine-binding capacity of the α globulin, probably a genetic trait. The possibility that a comparable mechanism would account for low protein-bound iodine with euthyroid state, high or normal protein-bound iodine with myxedema, and low or normal protein-bound iodine with thyrotoxicosis should be kept in mind.

535. Kitchin and associates of Liverpool followed up on the finding of Harris, Kalmus, and Trotter (1949) that nontasters of PTC are slightly more liable to develop nodular goiter than are controls, whereas a normal distribution

of PTC taste capacity is demonstrated by persons with diffuse toxic goiter. The long-recognized familial disposition to goiter and the goitrogenic properties of thiocarbamides make the findings of Harris, Kalmus, and Trotter very interesting. The Liverpool group found, in 246 cases of adenomatous goiter, a significantly higher proportion of *nontasters*, especially in men. In 133 patients with diffuse toxic goiter a significant excess of *tasters* was found, with no sex difference.

536. Dunning described *Hashimoto's disease* (struma lymphomatosa) in 2 sisters (aged 22 and 18 years) and one of their paternal first cousins (aged 19 years). Agar diffusion antibody tests were negative in all but were not performed until 4 to 5 years after surgical excision of the thyroid.

537. Parathyroids. Lobdell described an interesting case of congenital *absence of the parathyroid glands.* The infant died at 55 days, having shown the characteristic features of hypoparathyroidism, specifically tetany, from the first day or so of life. At autopsy no parathyroids were demonstrable. The thymus, which like the parathyroids develops from branchial pouches III and IV, was also absent. There were also agenesis of the thyroid isthmus and an anomalous vascular ring at the aortic arch area. One sibling was normal; there was no evidence for or against a genetic basis of the abnormality.

Roberts described a family in which 6 members (4 brothers and a son and daughter of one of them) showed calcification of the basal ganglia. One had epilepsy, one had recurrent severe depressions, and the others were symptomless. There were some indications of hypoparathyroidism, which Roberts felt was probably inherited as an autosomal dominant and was responsible for the calcification of the basal ganglion.

OL.
12
960

XV. EYE

538. Congenital microphthalmos with cyst formation seemed to be inherited as a recessive (Gill and Harris) (see ¶311).

Negrelli reported on *ocular albinism*, a sex-linked character which in heterozygous females has partial expression. Affected males have an albinotic fundus, visible choroidal vessels, hypoplasia of the macula, horizontal nystagmus, marked reduction in visual acuity, characteristic diaphaneity of the iris, and fair complexion. Carrier females have no symptoms and no objective defect in vision but show accumulations of dark brown pigment especially in the periphery of the fundus. The author gave an interesting resumé of five other conditions which affect the eye, which are sex linked, and which have mild expression in the heterozygous females: one form of retinitis pigmentosa, choroideremia, keratosis follicularis spinulosa decalvans, external ophthalmoplegia with myopia, and anhidrotic ectodermal dysplasia.

539. Schappert-Kimmijser, Henkes, and van den Bosch studied *Leber's amaurosis congenita* in the Netherlands as part of a survey of causes of blindness. (Not to be confused with Leber's optic atrophy, the disorder under discussion

is a tapetoretinal degeneration.) There were 114 cases in adults and 113 in children. In children, the authors estimated, this disease may account for as much as 18 per cent of blindness. Because of the emergence of other causes the proportion in adults is only about 3 to 8 per cent. The features were (1) blindness or near-blindness from birth, (2) discrepancy between the benign appearance of

Fig. 20*A*.—Xeroderma pigmentosum. D. P. (A28756), aged 26 months, shows the frecklelike, hyperkeratotic lesions of xeroderma pigmentosum and also a squamous cell epithelioma of the cheek. The parents were not related. Two siblings were normal.

fundus picture and the degree of visual impairment, (3) reduced electrical activity of the retina on photic stimulation (demonstrated by electroretinography), and (4) recessive inheritance. On an isolated island separated from the mainland until 1941, 13 cases were discovered in a population of about 4,000 persons.

540. Kjer, in one of the monographs from the University Institute for Human Genetics in Copenhagen, described his findings in nineteen families affected by one of the four types of *hereditary optic atrophy:* infantile optic atrophy with dominant mode of inheritance. The other three types in Kjer's view are (1) congenital optic atrophy with dominant transmission accompanied by nystagmus, (2) optic atrophy which is congenital or of early onset with recessive transmission, and (3) the form properly called "Leber's optic atrophy" in which the mode of inheritance is obscure. Kjer reviewed, in a useful manner, the literature on each of these four. Leber's authority was so influential that "many authors and clinicians . . . describe every hereditary optic atrophy as a case of Leber's disease." The clinical characteristics of the true Leber's disease,

according to Kjer, are (1) onset as bilateral optic neuritis (retrobulbar neuritis or neuroretinitis), (2) resulting partial, and only infrequently total, atrophy of the optic nerve, (3) onset between 12 and 30 years as a rule, and (4) predominant affection of males. He reviews the various views on its heredity: X-linked recessive inheritance, sex-limited autosomal dominance, and cytoplasmic inheritance. The last is suggested by the observation that perhaps only females transmit the disease or the carrier state. In Japanese, what seems to be the same disease occurs more commonly in women that it does in the Caucasian race in which women are much less often affected than men.

541. Giller and Kaufman reported *carcinoma of the cornea* in a patient with xeroderma pigmentosum. The parents were third cousins; the patient was the only one of 5 children affected (see Fig. 20).

Familial corneal degeneration (lattice type) was discussed by Frayer and Blodi. The disorder seems to be transmitted as a dominant trait.

Ahuja discussed the heredity of what he prefers to call "arcus corneae" to avoid the prejudicial connotations of such designations as "arcus senilis." He observed the change in young children of affected families and suggested that hyperlipidemia may not be the only mechanism for this trait.

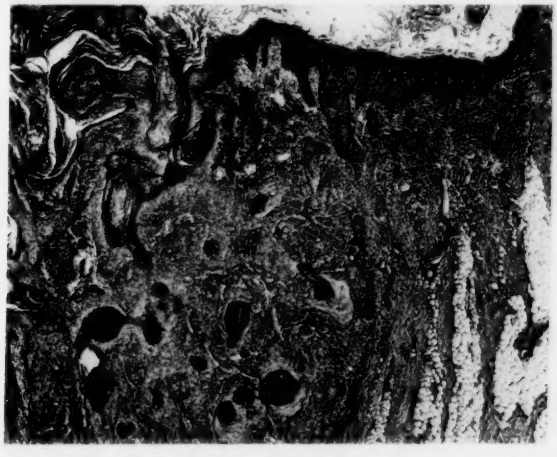


Fig. 20*B*.—Histologic studies revealed frank squamous cell carcinoma with invasion of the deeper structure of the skin. In the skin itself there were areas of atrophy and abnormal pigment deposits in the depths of the derma, as well as areas of hyperplasia of the deeper layers of the epidermis (×30; reduced one-third).

542. Several members of a family studied by Levitt showed *laxity of the lower lids* with little resistance to downward pull—the lower lid could be pulled almost to the level of the nostrils. No comment on joint laxity or other skin laxity was made.

543. Alström and colleagues described 3 cases of a syndrome which they believe is distinct from the Laurence-Moon-Bardet-Biedl syndrome and has not

previously been described: retinitis pigmentosa, obesity, diabetes mellitus, and neurogenous deafness. They pointed out, interestingly, that retinitis pigmentosa can result from mutation at no fewer than eight different loci and probably more. The only respect in which their cases differed from what is considered to be the true Laurence-Moon-Bardet-Biedl syndrome was the absence of polydactyly, mental retardation, and hypogenitalism. However, in the one case in which testicular biopsy was done, some degree of tubular sclerosis was in fact found. We are not convinced that the authors have proved their case for a distinct entity. The inheritance seemed to be autosomal recessive; the 3 affected persons were related.

Several case reports of the Laurence-Moon-Bardet-Biedl syndrome appeared (Pahwa and Singh) (see ¶'s 554, 589).

544. Cole found *unilateral amblyopia* (unilateral reduction in visual acuity without evident pathologic basis) in over 5 per cent of 10,000 individuals subjected to eye examination. Family histories suggested a genetic basis. Further study of the genetics was urged.

VOL. 12 1960

545. Maumanee has proposed a new theory for the mechanism of *congenital glaucoma*. Tonographic, histologic, and gonioscopic findings indicate that in most cases the elevated intraocular pressure is *not* due to (1) absence of Schlemm's canal, (2) presence of an unabsorbed membrane over the trabeculae, (3) a block of the angle by adhesions, or (4) a defect in the collector channels. Maumanee's theory proposes that the increased pressure is due to an abnormal insertion of the longitudinal and circular bundles of the ciliary muscle into the trabecular fibers, so that contraction of these muscles either narrows Schlemm's canal or at least fails to open it.

546. Macklin reported on an intensive study of a large number of families of *retinoblastoma* probands. The finding in many of these families of distant relatives with retinoblastoma casts doubt on the interpretation of the inheritance as simple autosomal dominant and on the mutation rates which have been estimated.

547. Kaufman and Thomas described pathognomonic opacities in the vitreous in cases of *familial primary amyloidosis*.

548. Walls and Heath described *ectopia lentis et pupillae* behaving as a dominant character with variable expression. For example, a mother had both whereas 2 sisters and her son had only ectopia lentis.

XVI. GENITAL SYSTEM

549. A wide spectrum of gonadal anomalies has long been recognized and these have been divided into different syndromes on purely clinical grounds. Gonadal dysgenesis has been used as a generic term for these conditions (Wilkins).

At one end of the spectrum is gonadal aplasia with complete failure of gonadal development, while in gonadal dysplasia the gonadal failure is not quite complete. The designation "the Turner syndrome" is applied to many members of these two categories but most commonly to gonadal aplasia. Next come the true hermaphrodites and the pseudohermaphrodites. The latter include congenital adrenal hyperplasia (see ¶530) and the syndrome of testicular feminization. At the other end of the scale are "primitive tests" and the Klinefelter syndrome, which has also been called "testicular dysgenesis" and "primary microorchidism". During 1959, cytogenetic studies revealed that two of these syndromes, Turner's and Klinefelter's, are associated with aneuploidy, namely, 2n = 45 and 47 with XO and XXY sex chromosome complements, respectively. Two true hermaphrodites have been shown to possess 46 with XX sex constitution, while a series of patients with testicular feminization had 46 and an XY chromosome complement. For further details see the previous section, "Cytogenetics in Man" (¶380 ff.).

Recent experimental work by Jost, by Witschi, and by others has indicated that while the development of the gonadal cortex is dependent on the presence of 2 X chromosomes and the medulla on the presence of a Y chromosome, that of the genital ducts is controlled by a locally diffusing organizer. In the absence of a male determining factor differentiation is female in type. On this basis Stewart suggested that the Turner syndrome could be called "cortical gonadal dysgenesis" and the Klinefelter syndrome "medullary gonadal dysgenesis." True hermaphrodites would then have corticomedullary dysgenesis.

A general review of sex aberrations has been given by Steiner. The genetics was reviewed by Stewart.

550. Gonadal aplasia (the Turner syndrome). Haddad and Wilkins reported on the nongenital anomalies of 55 patients with gonadal aplasia. All were short in stature but bone age was normal. About half had webbed neck. In 13 the webbing was characterized by loose folds of skin at the nape and sides of the neck (Bonnevie-Ullrich type, in the authors' terminology). In the others the webbing was of the "tight" pterygium type of Turner. Change from the Bonnevie-Ullrich type to the Turner type by early childhood occurred in 7. Aortic coarctation was present in 8, all cases with webbed neck. In 2, subaortic stenosis was associated with coarctation. In 3, cardiovascular anomalies (subaortic stenosis, ventricular septal defect, or dextrocardia) occurred without coarctation. Cutis laxa (10 cases) and edema of the extremities occurred only in cases with webbed neck. Pitting edema, often asymmetric, persisted into adult life, the oldest patient being 25 years old. Similarities to Milroy's disease are suggested. In fact, one patient who did not have an abnormal neck developed progressive edema of the right leg beginning at 7 years of age and persisting into adult life; the edema was labeled Milroy's disease in this patient. Keloid formation was frequent. Shieldlike chest with wide intermammary distance, cubitus valgus, and abnormal facies (micrognathia, epicanthus, low-set ears, and high-arched palate) and nails (narrow with square ends and increased lateral curvature) occurred with and without webbed neck. All patients with webbed neck were chromatin negative; of 11 patients with a normal neck in whom a test was made, 4 were chromatin

positive. In 24 out of the 47 cases there was rarefaction of the bones ("osteoporosis"), possibly due to deficiency of the sex hormones (cf., postmenopausal osteoporosis), but administration of estrogens over a long period produced no apparent change. Unexplained moderate hypertension occurred in 14 patients who did not have coarctation. Multiple angiomata of the bowel were present in 4 patients with resulting melena and anemia. Eight of 55 patients had severe mental retardation on purely clinical evaluation. However, 3 out of 20 patients tested had IQ's over 120. Family history disclosed no other cases among the relatives of the 55 probands. However, in the discussion the authors mentioned five families in which 2 siblings had the Turner syndrome, 2 sets of twins concordant for the trait, and a few instances of affected collateral relatives.

Analysis of congenital anomalies associated with chromosomal aberrations may have importance in assignment of gene loci to specific chromosomes.

Archibald, Finby, and De Vito pointed out the "metacarpal sign" present in the great majority of patients with both chromatin-negative and chromatin-positive gonadal aplasia (17 cases). Shortness of the fourth metacarpal relative to the third and especially to the fifth constitutes this sign. They also pointed out (1) that the sign may occur as a family characteristic without endocrinologic significance, (2) that cases of the Klinefelter syndrome do not show the sign, (3) that males with gonadal aberrations such as delayed descent of the testes frequently show the sign, (4) that the sign is more striking in the left hand than in the right, and (5) that persons with the sign tend to be of short stature.

The nature of the rare "male Turner's" (e.g., Flavell: Brit. J. Surg. 31:150, 1943) is of interest and will probably be elucidated in due course. Silver described 2 cases of congenital hemihypertrophy, short stature, and elevated urinary gonadotropin in boys. One case had nonpitting edema of the dorsa of both hands and feet, moderate cubitus valgus, slight increase in the amount of skin of the back of the neck, cryptorchidism, and wide spacing of the nipples.

Case reports were provided by Naidu and Nehdi.

Hutchings described a 13-year-old phenotypic female who was amenorrheic and short of stature but had none of the other external features of the Turner syndrome. The ovaries were grossly normal as were the Fallopian tubes and uterus. Biopsy of the ovary showed primary follicles. However, the patient was chromatin negative on buccal and vaginal smears. The patient, however, also suffered from a malabsorption syndrome which could well be responsible for the dwarfism and delayed maturation. Confirmation of the claim that this patient is chromatin negative by additional methods is clearly desirable.

Elliott, Sandler, and Rabinowitz described 3 sisters, aged 23, 25, and 27 years, with primary amenorrhea but no other stigmata of the Bonnevie-Ullrich-Turner syndrome, female nuclear chromatin pattern, and marked osteoporosis. Laparotomy in one patient showed primitive gonadal ridges with some resemblance to ovarian stroma and also some tubules, thought to be mesonephric in origin. Serum acid phosphatase was elevated. The authors "suggested that these bony changes constitute an incomplete form of osteogenesis imperfecta." This suggestion, said to be "the modern view," only confuses the understanding of both osteogenesis imperfecta and gonadal dysgenesis. Osteoporosis is frequent

VOL. 12 1960

in both chromatin-positive and chromatin-negative gonadal aplasia. The report (Gebala: Lancet 2:1084, 1956) of elevated serum acid phosphatase in osteogenesis imperfecta requires further evaluation. The authors quote Hoffenberg and Jackson (1957) as describing blue sclerae in their cases of gonadal dysgenesis. However, this cannot be taken as indicative of any basic relationship to the true hereditary osteogenesis imperfecta; blue sclerae tend to occur with any severe osteoporosis such as senile osteoporosis and Cushing's disease (personal observations).

551. True hermaphroditism. See ¶385 for chromosome studies.

552. The syndrome of testicular feminization (¶372). Lubs, Villar, and Bergenstal reported a family in which all 5 males (so identified by nuclear sex) in two sibships of two successive generations had male pseudohermaphroditism of the feminizing testis type. The pedigree supports the thesis that the trait is either a sex-linked recessive or a sex-limited autosomal dominant, as suggested by Grumbach and Barr (see ¶'s 210, 372).

L.
2
60

Jacobs and colleagues found that the diploid chromosome number in these patients is 46 and that the chromosomal sex constitution is XY. Corroborative evidence was provided by Stewart who found color blindness in 2 unrelated patients with the syndrome; neither parent of the 2 patients was color blind. The distribution of color blindness and the syndrome of testicular feminization in this family suggests that the two traits are not closely linked and that testicular feminization may be a sex-limited autosomal dominant character, rather than a sex-linked recessive character (¶210). Specifically, in one of the families studied by Jacobs and by Stewart one sibling had the syndrome and color blindness, one had only the syndrome, and a third, a normal male, had only color blindness. If the "female" hemophiliac reported by Nilsson (¶385) had the syndrome of testicular feminization further evidence against sex-linkage is provided: a brother of Nilsson's patient had only hemophilia.

553. The Klinefelter syndrome. The prepubetal lesion in the testis was found to be a marked reduction in the complement of spermatogonia (Ferguson-Smith). Tubular hyalinization was found in only the oldest (aged 12 years) of 8 patients. The 8 patients were 1.2 per cent of 663 phenotypically male mentally retarded children in special schools in Glasgow; all 8 were chromatin positive.

Moore found chromatin positivity in 5 of 3,715 newborn "male" infants. All of 1,804 newborn "female" infants were chromatin positive.

Roland, Rogers, and D'Agincourt described a case of chromatin-positive Klinefelter's syndrome with spider angiomata. Urinary estrogen excretion seemed to be only in the range expected of a normal female. Therefore the mechanism of the angiomata is not entirely clear—at least the mechanism suggested by Bean (1945) for the spider angiomata in hepatic cirrhosis could not be shown to be operating. Roland also reported on another case with some discrepancy between the nuclear sex as estimated from tissue sections and buccal smears compared

with the low drumstick count on the polymorphonuclear leukocytes—a finding reported previously by others. This patient also showed an unusually high estrogen excretion which, like the previous case, was in the range for normal females.

In a comprehensive review of the subject of male hypogonadism Nowakowski discussed chromatin-positive Klinefelter syndrome and the hypogonadism of the Werner syndrome, myotonic dystrophy, and the Laurence-Moon-Bardet-Biedl syndrome. Familial hypogonadism was also reviewed. Nowakowski, Lenz, and Parada also reported on 40 cases of chromatin-positive Klinefelter syndrome. They tested color vision in 34 and found 3 cases of color blindness. In 1944 Kallmann and Barrera (J. Ment. Deficiency 48:203, 1944) described a syndrome of eunuchoidism, anosmia, and mental deficiency in 12 related males. The results of chromosome studies will be awaited with interest.

Mosier, Scott, and Cotter found chromatin positivity in 0.79 per cent of male inpatients of a California institution for mental defectives. The lower figure than those of Ferguson-Smith (see preceding) and of Prader may be related to the fact that these were most severely retarded persons. Stigmata of Mongolism were present in one of 7 chromatin-positive patients and a second had a Mongoloid half sibling.

Many persons with the true Klinefelter syndrome have normal intelligence. As described by Rabson, Jacob Erdheim (1874-1937), a Viennese pathologist known to medicine for cystic medial necrosis of the aorta and other pathologic descriptions, seems to be a case in point:

> ". . . Erdheim towered above the others. Despite his great height, his head was of normal size. . . . The face, in keeping with his disability, was an odd blend of adolescent boy and old woman, and the skin, covered by a delicate, barely perceptible fuzz, was soft and faintly brown. His arms were disproportionately long, as were the broad fingers. . . . The wide pelvis easily supported the drawstrings of his white cotton trousers. Excessively long, his legs terminated in the largest pair of feet yet known to me. . . . He spoke a soft Austrian German in a pleasant tenor voice. . . . His life centered in the hospital, and it was his home as well. In his quarters in the same building with the resident staff, the light shone at night and before dawn on winter days. . . . Undoubtedly, the perfectionism was aggravated by lack of those benign influences associated with a normal endocrine apparatus. . . .
>
> [The autopsy.] The penis was small (2 × 1.5 cm.), as was the glans. The testes, located in the inguinal canals close to their exits, were infantile (bean-sized) and composed of 'pale-gray, gelantinous' tissues. It was reported that the prostate was strikingly small, and each spermatic cord was infiltrated with fat. While the right breast was grossly made up of fat, the left also included gray tissues, apparently glandular."

The cause of death was extensive coronary atherosclerosis.

Stewart reporting on 5 cases pointed out that 4 of them had eunuchoid proportions despite early closure of the epiphyses. Tanner and associates investigated the skeletal age in young patients with the Klinefelter and Turner syndromes to determine whether they followed the normal maturation curves for boys and girls. They found that the patients with the Klinefelter syndrome with an XXY chromosomal constitution had a skeletal age equivalent to normal males with an XY pattern. The patients with the Turner syndrome (XO) had a bone age approximately equivalent to normal females (XX). They concluded that genes on the Y chromosome are responsible for the sexual dimorphism in rate of normal

development. They also noted that in the Klinefelter syndrome the children had abnormally long legs though their trunk length was normal. As it was present before puberty, a fundamental difference in growth rate was suggested as the explanation.

Miscellaneous: 554. Alström and colleagues mentioned in passing that a female chromatin pattern was found in a phenotypic male with the Laurence-Moon-Bardet-Biedl syndrome (obesity, polydactyly, mental retardation, retinitis, pigmentosa, and hypogenitalism) (see ¶'s 543, 589).

555. Bunge and Bradbury described 2 unrelated boys, aged 4 and 6 years, with *an unusual syndrome:* unilateral undescended testis containing round bodies in the seminiferous tubules, reduplication of the great toe in one and the thumb in the other on the same side as the cryptorchidism, hyperteleorism, and in the descended testis primary spermatocytes (which are said to appear normally at 12 to 14 years).

OL.
12
960

556. Rümke and Hellinga found agglutinating autoantibodies (in a titer of 1:32 or more) against spermatozoa in about 3 per cent of 2,015 males from sterile couples. Of 416 fertile men none showed autoantibodies. In their discussion they suggested that stasis in the vas deferens or epididymis might be responsible for the formation of autoantibodies. They pointed out that the autoantibody appears in the semen. Weil and Finkler discussed the isoantigenicity of rabbit semen.

557. Ashley examined the question of whether *ovarian pregnancies* are parthenogenetic by determining the nuclear sex of the fetal portion of 12 such pregnancies. Seven were chromatin negative ("male") and 5 were chromatin positive ("female"). He concluded that ovarian pregnancies are not parthenogenetic but that fertilization must precede ovarian implantation of the zygote. Of two alternative possibilities, haploidy was considered an unlikely explanation for the male nuclear sex cases since visual examination of the Feulgen-stained preparations suggested that the amount of DNA in each cell was "normal." Evaluation of the other alternative, that the chromatin-negative fetuses are XO as in gonadal aplasia, will require specific studies of the chromosomes.

XVII. MUSCLE

558. Zellweger and Bell listed four forms of *congenital muscular hypertrophy:*

a. Congenital muscular hypertrophy associated with brain disease
b. Thomsen's myotonia congenita
c. Muscular glycogenosis
d. Benign idiopathic congenital muscular hypertrophy

559. Progressive muscular dystrophy. Lisan, Imbriglia, and Likoff reported on myocardial disease in 2 cases of muscular dystrophy. The first patient was a 19-year-old male with perfectly classic pseudohypertrophic muscular dystrophy.

Despite the well-recognized myocardial involvement in this case and the typical clinical features, both cardiac and extracardiac, thoracotomy with biopsy of the atrial and ventricular myocardium was performed! The second patient, a 58-year-old woman, had muscular dystrophy of uncertain type but certainly different from that in the first case. It is not certain that the heart disease was related to the disease of skeletal muscle. The following dubious statement is made: "As a matter of fact, the presence of a muscular wasting disease existing from childhood or puberty with chronic congestive heart failure in a middle-aged woman strongly suggests the diagnosis of progressive muscular dystrophy." Long survival, predominant involvement of females, and cardiac involvement are not all features of any variety of progressive muscular dystrophy known to the reviewers. Levin, Baens, and Weinberg described the cardiac involvement in classic cases of pseudohypertrophic muscular dystrophy of the Duchenne type.

Patterson and Rios described involvement of the smooth muscle of the gastrointestinal tract.

Bourne and Golarz found that the connective tissue in cases of pseudohypertrophic muscular dystrophy actively dephosphorylates diphosphopyridine

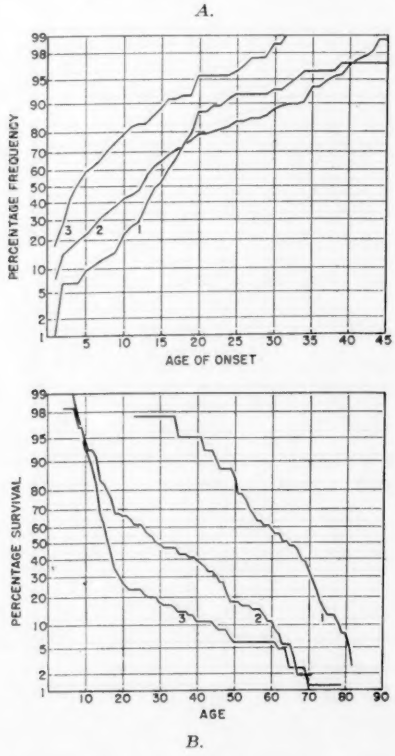


Fig. 21.—Natural history of three types of progressive muscular dystrophy: (*1*) probably dominant form (facioscapulohumeral), (*2*) probably recessive form (limb-girdle), and (*3*) probably sex-linked form (Duchenne pseudohypertrophic). *A*, Cumulative distribution of age of onset among affected persons. *B*, Probability of survival until age *x* among dead patients. (From Chung, C. S., and Morton, N. E.: Am. J. Human Genet. 11:339, 1959.)

nucleotide and to a lesser extent triphosphopyridine nucleotide. Three possible explanations come to mind: (1) Normal leakage of these metabolically important phosphate compounds from the muscle and destruction by connective tissue may deprive muscle of them. (2) The fundamental defect may reside in the muscle membrane. Diffusion of the phosphate esters into the surrounding milieu may evoke adaptive synthesis of enzymes in connective tissue to dispose of them. (3) Excessive production of the hydrolytic enzyme may lead to their penetration of the muscle, with disruption of normal muscle metabolism.

In the last decade studies in several parts of the world have contributed information on the confused questions of the classification and formal genetics of the several types of progressive muscular dystrophy: Tyler and colleagues in Utah (1950, 1951), Levison in Denmark (1951), Stevenson in Northern Ireland (1953, 1955), Becker in Baden, Germany (1953), Walton in Newcastle, England (1954), Lamy and de Grouchy in Paris (1954), and others, including Chung and Morton in Wisconsin (see below). To these Blyth and Pugh added a survey in the region of Leeds, England. The studies indicate that clinical and genetic analysis has gone as far as is possible until biochemical methods of study and classification become available.

Blyth and Pugh found 83 families in which 106 affected persons were examined. These could be classified in the following manner:

a. Childhood type (seventy-eight families with 96 patients examined), which fell into two subgroups:

1. Severe group with fifty-six families and all patients boys. In this group, genetically homogeneous, the disease behaves as a sex-linked recessive trait.
2. Mild group with twenty-two families and both sexes affected. This group is genetically heterogeneous with sex-linked recessive, autosomal recessive, and autosomal dominant transmission probably involved in separate instances.

b. Adult type (five families with 10 patients). Again probably heterogeneous genetically, this group was probably dominant in three families and recessive in two.

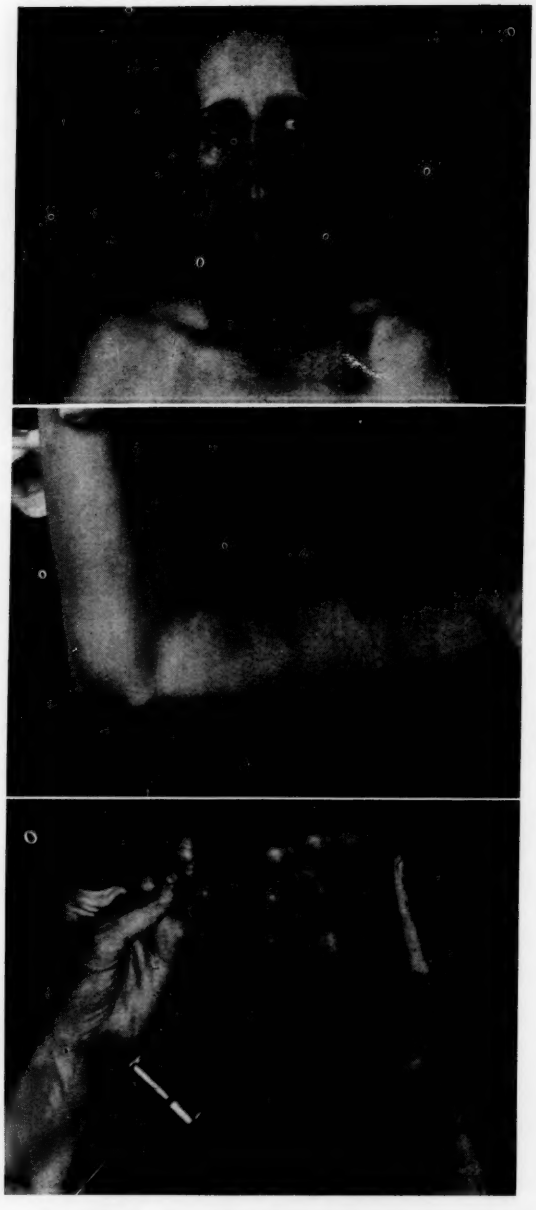
Chung and Morton applied the method of discriminant functions to a large body of data on various types of muscular dystrophy collected from the literature and in the Muscular Dystrophy Clinic in Wisconsin. On the basis of pedigrees, an initial five-way classification was made:

a. Parent and child affected (possibly dominant)
b. Not so; affected girl in the pedigree (possibly recessive)
c. Not so; maternal male relative affected (possibly sex linked)
d. Not so; only brothers affected (possibly autosomal or sex linked)
e. Ambiguous or doubtful

The data on age of onset and on survival in the first three groups are interestingly demonstrated in Fig. 21.

Morton and Chung studied the formal genetics of muscular dystrophy in four groups:

a. Facioscapulohumeral muscular dystrophy is an autosomal dominant trait with complete penetrance in individuals of both sexes who survive to the age of onset. The prevalence was estimated at about 2 living patients per million



A.

B.

C.

Fig. 22.—Myotonic dystrophy. D. L. (702565) was 38 years old at the time of these photographs. Several members of her family in at least three generations have had cataract, "stiff legs," and difficulty in swallowing and walking. Alcoholism, suicide, and criminality also seem to be unusually frequent in this family. The patient has had progressive loss of hearing, trouble swallowing, and weakness of the arms, legs, and neck. Menarche was late, at age 18. I^{131} studies of thyroid function indicate hypothyroidism. *A*, Note the myopathic facies, temporal balding, and muscular atrophy especially in the temporal and sternocleidomastoid muscles. *B*, Note the myotonic response to percussion of the biceps muscle. *C*, Note the myotonic response to percussion of the thenar eminence.

VOL. 12 1960

persons and a frequency, in each million births, of about 4 persons destined to develop the trait. Fertility is little reduced and the mutation rate is not more than five per ten million gametes.

b. Limb-girdle muscular dystrophy is an autosomal recessive trait with equal penetrance in males and females, with a prevalence of about 12 living patients per one million persons, and a frequency, per one million births, of 38 persons who will develop the disease. Fertility is about 25 per cent of normal. The frequency of heterozygous carriers is about 0.016.

c. Sporadic limb-girdle muscular dystrophy has clinical and fertility characteristics like the recessive type. The prevalence is about 8 living patients per one million and the incidence at birth about 27 persons. If these cases were all due to the occasional expression of the gene in heterozygous state, the penetrance would be only 0.0017. The cases are seemingly not due to dominant mutation, since all of 110 children of such patients were normal.

d. Duchenne pseudohypertrophic muscular dystrophy is a sex-linked recessive trait with a prevalence of 66 living patients per one million males and an incidence at birth of 279 boys per one million male births. Fertility is less than 4 per cent of normal. One third of cases are due to new mutation which occurs at a rate of about 89 per one million gametes and is the same in eggs and sperm. There is no elevation of maternal age in sporadic cases.

Asmundson and Julian (1956) described an autosomal recessive variety of muscular dystrophy in New Hampshire chickens. Cornelius and associates found elevated plasma aldolase and glutamic oxalacetic transaminase activities in affected birds.

560. Isaacs described a mother and her son and daughter with *myotonia congenita* Thomsen. Quinine, local procaine, procaine amide, insulin, injections of 50 per cent magnesium sulfate, curarization, sodium loading, and sodium depletion were without effect on the mother's myotonia. However, marked improvement occurred when potassium depletion was achieved with cortisone and chlorothiazide. The dauthter was treated with chlorothiazide only and also improved. An unrelated case of myotonia congenita and a case of severe dystrophia myotonica showed dramatic improvement on cortisone and chlorothiazide.

561. Kilburn and colleagues demonstrated the typical "hypoventilation syndrome" in cases of *myotonic dystrophy.* Minute ventilation was decreased, there was carbon dioxide retention, and responsiveness to administered carbon dioxide was reduced. Administration of oxygen had ill effects, as demonstrated by reduced ventilation and increased carbon dioxide retention. Pulmonary hypertension developed in some. The demonstration of involvement of the diaphragm by Caughey and Pachomov correlates well with the physiologic findings.

Marshall found "testicular degeneration" in biopsies of 4 out of 5 cases of males with myotonic dystrophy (see Fig. 22).

562. Jones, McSwiney, and Brooks, in 2 cases of *familial periodic paralysis,* confirmed the relationship of potassium shifts to attacks of weakness but were

unable to corroborate any necessary relationship of sodium shifts or of aldosterone secretion to attacks. Conn (1957) had suggested the latter possibility. Sagild studied potassium metabolism in, and the genetics of, hereditary episodic adynamia and familial periodic paralysis. In the first, potassium is high during attacks; in the second it is low. (It is amusing to observe that the titles of the two diseases are really identical: "hereditary" and "familial," "episodic" and "periodic," and "adynamia" and "paralysis" are essentially synonymous.) Sagild's family studies were sufficiently extensive to demonstrate that two seemingly unrelated pedigrees were derived from a common ancestor more than 200 years ago. As one might expect, patients with either of these diseases are likely to be suspected of psychoneurosis or of malingering. Conversely, others, knowing their family histories, induce attacks for the purpose of malingering! Sagild reviewed, in addition to his own collection of cases, more than 700 cases from the literature. Egan and Klein reported on three unrelated families with the hyperkalemic variety of periodic paralysis.

VOL. 12 196

563. Myasthenia gravis. Walsh and Hoyt reported on congenital and presumably hereditary myasthenia gravis in 4 brothers. The only other siblings, 2 girls, were normal. They suggest that the disease is that described by Levin (1949). It differs from classic myasthenia gravis (of Erb and Goldflam) in its congenital and familial nature and lack of progression or remissions. The response to Prostigmin is dramatic.

564. Case reports of *myoglobinuria* included those of Gillett, of Segar, of Kaufman and Barry, and of Korein, Coddon, and Mowrey. In a long review Kähler discussed all aspects of myoglobinuria and surveyed in detail the subject of idiopathic paroxysmal paralytic myoglobinuria (hereditary paroxysmal rhabdomyolysis). Javid, Fischer, and Spaet concluded that the haptoglobins do not bind myoglobin. In serum containing myoglobin the mobility of the haptoglobins on starch gel electrophoresis was not altered. There was no quantitative change in the haptoglobins during attacks of paroxysmal rhabdomyolysis.

565. In 1951 McArdle (Clin. Sc. 10:13, 1951) of Guy's Hospital, London, described a skeletal "myopathy due to a defect in muscle glycogen breakdown," manifested by life-long pain, weakness, and stiffness of muscles after slight exertion. These symptoms developed more quickly if the muscles of a limb were rendered ischemic before the exercise. Studies reported by Mommaerts and colleagues, by Larner and Villar-Palasi, and by Schmid, Robbins, and Traut demonstrated virtual absence of phosphorylase activity. Other enzymes related to glycogen metabolism were present, and the glycogen had a normal, branched structure. The glycogen content of skeletal muscle was increased. UDPG-glycogen transferase was demonstrated; glycogen synthesis in the absence of phosphorylase was attributed to the latter enzyme. The clinical, histologic, and chemical features were described in detail in one case by Schmid and Mahler under the title of "Chronic Progressive Myopathy With Myoglobinuria." (Myoglobinuria was not noted in McArdle's case.) The 54-year-old man had had symptoms for 35 years.

He could perform minimal muscular work without limit, but even moderate physical effort resulted in prolonged, painful cramps, necrosis in the muscles used, and transient myoglobinuria. A defect in glycolysis was suggested by the failure of exercise to produce the expected rise in venous lactate concentration. The glycogen content of muscle was about five times increased over normal. Incubation of muscle homogenate resulted in four times less lactate production than in controls. Addition of phosphorylase corrected this defect. With glucose-1-phosphate as a substrate, lactate production by the patient's muscle was normal, further suggesting that the defect concerns the phosphorylase system which catalyzes the breakdown of glycogen to glucose-1-phosphate. As a result of this enzymatic defect, anaerobic glycogenolysis is eliminated as a source of energy for muscle contraction. Muscular work is limited by the energy which can be derived from nutrients diffusing from the blood into the muscle cell.

OL.
12
960

XVIII. NEOPLASMS

See also lipomata (¶623), stomach cancer (¶495), retinoblastoma (¶546), neurofibroma (¶572), intestinal polyposis (¶'s 435, 439), and prostatic cancer (¶325).

566. Way, Hetherington, and Galloway described carcinoma of the cervix in 3 sisters.

567. Macklin published data indicating that grandmothers, mothers, aunts, and sisters of women with *breast cancer* have breast cancer with a frequency significantly greater than that of women in a similar age range either in the general population or in two control samples. The effect was observed in both paternal and maternal grandmothers and aunts. Biased selection, chance distribution in the population, and better recall by women with breast cancer would not, seemingly, account for the data. The ratio of observed to expected number of breast cancers was higher in unmarried than in married aunts and sisters—a fact interpreted to illustrate a collaboration of genetic and extrinsic factors.

Murphy and Abbey studied the families of 200 surviving women with breast cancer (of ages 40 to 65 admitted to Philadelphia hospitals in the 5 years preceding the study) and of 200 control women who were of the same age and admitted to a dental clinic in the same period of time. The possible sources of bias in such a study and the steps taken to avoid them were described. The study was confined to two generations, that of the proband and that of her parents. The authors could find no evidence of familial aggregation for breast cancer or any other form of cancer in these families. They conclude that if any familial tendency exists it must not be large enough to be detected in a study of this size. In the rare instances in which there was a statistically significant difference between the cancer and control groups with respect to the frequency of cancer, it was found in more remote rather than closer relatives and the higher frequency of cancer was in the control group rather than the cancer group. For this, the best explanation was held to be that they represent the occasional

chance differences which the criteria of significance blindly label as significant. Anderson (Am. J. Human Genet. 11:388, 1959) suggested that limiting probands to the 40 to 65 years of age group may account in part for the lower cancer frequency among relatives. Since the mean age of siblings would be lower, the risk of cancer is less. He also made the point that siblings are the most meaningful group since "when considering a condition as common as cancer, the cancer frequency among cousins would be expected to approach that of the population from which the families were drawn."

Childbearing is another important factor influencing the occurrence of breast cancer (Macklin). The highest frequency of breast cancer was found in nulliparous women, with decreasing frequency of the disease as the number of pregnancies increased. Nulliparous women closely related to a woman with breast cancer had more breast cancer than nulliparous women in the general population.

568. In the mouse, Vlahakis and Heston purport to have demonstrated (1) an association between the gene for *obesity* and a reduction in susceptibility to pulmonary tumor and (2) a positive correlation between pulmonary tumors and muscular and skeletal development as revealed by body length, femur length, and muscle weight. They commented that "it would be interesting to know what correlations exist in man in respect to neoplasms."

569. Cameron described three families with multiple cases of *mixed salivary tumors*. The families contained 7 cases, these being in a total series of 401 cases of such tumors.

570. Galton and Benirschke found, in a *teratoma* in a 24-year-old woman, that the diploid chromosome number was 46 and the sex constitution XX (¶387). In males with teratoma of the testis (Leading Article) about half of cases show chromatin-positive and half show chromatin-negative tumors. Myers, in Willis's material, found that in thirty-three testicular teratomata there were thirteen male, ten female, and eight mosaics by nuclear sexing. In the remaining two, there was double sex chromatin. Among eight teratomas at other sites in males, one, from the mediastinum, showed female sex chromatin. Sixty-four teratomas from females all had female sex chromatin. Obviously, further chromosome studies are required.

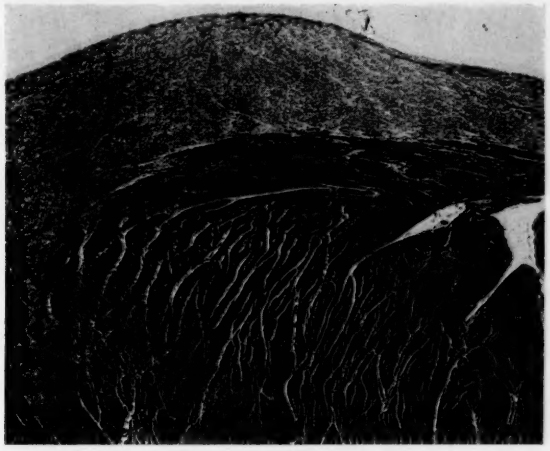
571. Razis, Diamond, and Craver found a slight familial aggregation with reference to *Hodgkin's disease*. They estimated that the risk to "close relatives" of probands is about three times the general risk. They quite properly point out that the familial aggregation is not impressive and that its basis, assuming it is real, need not be genetic.

XIX. NERVOUS SYSTEM

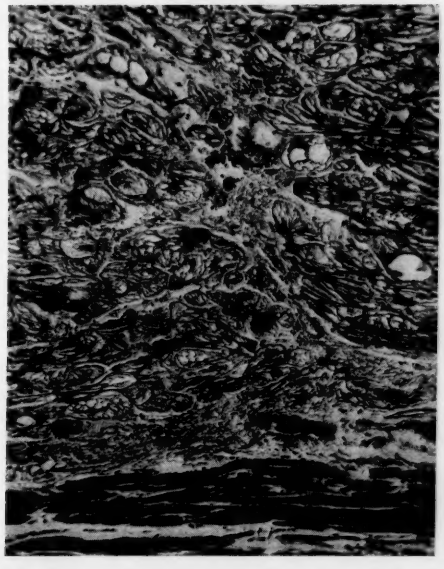
Phacomatoses: 572. Hillensis reported 3 cases of intrathoracic meningocele in association with *von Recklinghausen's disease* (*neurofibromatosis*). Of 33

Fig. 23.—A Negro family with tuberous sclerosis. The proband J. P. (564820; aut. 22957), a Negro male, died at the age of 10 years of the effects of brain tumor. Fits began at 3 ½ years. Adenoma sebaceum was first noted at 5 years. The cerebrospinal fluid always showed marked elevation of protein. Autopsy revealed glioma of the subependymal tissue of both caudate nuclei and a cyst in the head of the left caudate nucleus. The kidneys were affected by multiple cystic myolipoangioadenomata. There was ectopic pancreas in the intestinal wall. Both lobes of the thyroid showed changes suspicious of carcinoma.

Scattered throughout the myocardium were a number of small white nodules of irregular shape. There was a single larger, rather soft subendocardial mass in the left ventricle below the aortic valve.



A.



B.

Figs. 23*A* and 23*B*.—Histologically, the myocardial tumors were typical rhabdomyomata with characteristic spider cells.

C. *D.*

Fig. 23*C* and 23*D*.—The mother of the proband (M. P., 284408), now 39 years old, has many manifestations of tuberous sclerosis. The most incapacitating are shooting pains, twitching, and weakness in the left leg beginning at the age of 21 years. She is normally intelligent with a calm, relaxed personality. The left leg shows hyperactive deep tendon reflexes with moderate spasticity. Recently there has been mild urinary incontinence. Adenoma sebaceum is distributed on the face and over the back of the shoulders in areas typically affected by acne. It is remarkable how little the lesions of the face have changed in the 11 years between the photographs in *C* and *D*. On the palm of the left hand and anterior aspect of left thigh there are soft, subcutaneous tumors about the size of a half dollar. These feel like lipomata.

Fig. 23*E*.—Subungual fibromata are striking on the toes (and also the fingers).

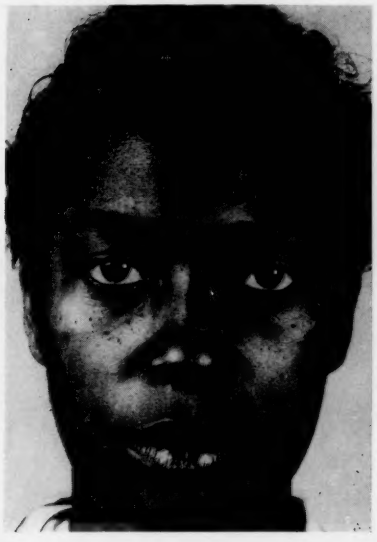


Fig. 23*F*.—A maternal aunt of the proband (E. W., 417620) appears to have tuberous sclerosis in exceedingly mild form. The only signs are lesions of the face, consistent with adenoma sebaceum. She is normally intelligent and otherwise normal.

cases previously reported in the literature, about 70 per cent had associated neurofibromatosis. In almost all, the preoperative diagnosis was neurofibroma of the posterior mediastinum. Bunner described 2 cases of lateral intrathoracic meningocele in patients with neurofibromatosis. In both the lesion was asymptomatic and was only detected incidentally on "routine" chest x-ray. Spinal air injection demonstrated filling of the "tumor." Progressive enlargement of the meningocele and erosion of vertebral bodies and arches and of the ribs is apparently related to pulsations in the spinal fluid with each heart beat—a mechanism comparable to that of the similar effects of aortic aneurysm. Kyphoscoliosis is frequent in these patients. Why patients with neurofibromatosis should develop this complication is not entirely clear. Judging from the usual asymptomatic state and from the surgical difficulties described in the literature, surgical attack should probably be undertaken only rarely. Sanmons and Thomas reported a case of the even rarer anterior lumbar meningocele: A 27-year-old sailor who had engaged in strenuous physical activity without discomfort developed low back pain. Typical cutaneous stigmata of neurofibromatosis were present. X-rays revealed deep scalloping of the posterior portion of the vertebral bodies with marked thinning of the pedicles from T_{10} to L_4. As in aortic an-aneurysm the resilient disk was unaffected. Myelograms showed herniation of the meninges. This is the first reported case of lumbar meningocele in neurofibromatosis.

Neurilemmoma of the tongue may occur as an isolated lesion or in a minority of cases may be a feature of neurofibromatosis (Mercantini and Mopper).

Fig. 24.—Tuberous sclerosis with brain, heart, and kidney involvement. P. L. P. (A70199), one of fraternal twins, died at the age of 7 months. The family history was negative. Tuberous sclerosis was not diagnosed clinically. A large mass was easily palpable in both flanks of the abdomen. The blood pressure was 196/140 mm. Hg. Convulsions occurred terminally.

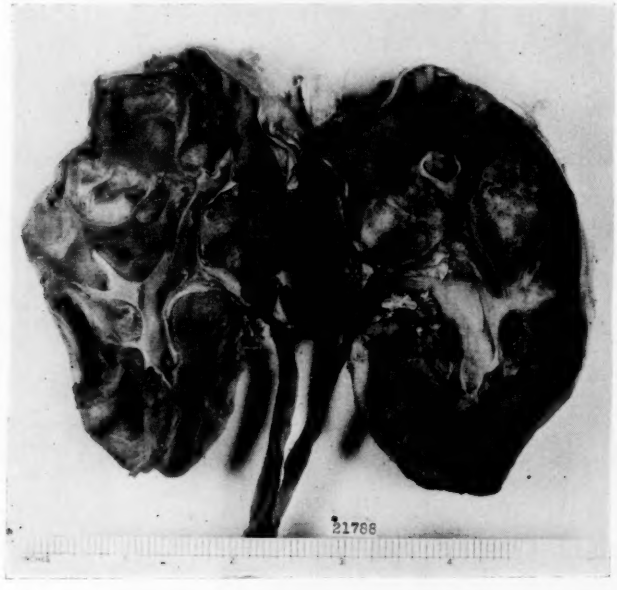


Fig. 24*A*.—At autopsy, the kidneys were found to be affected by what morphologically would pass for classic congenital cystic disease.

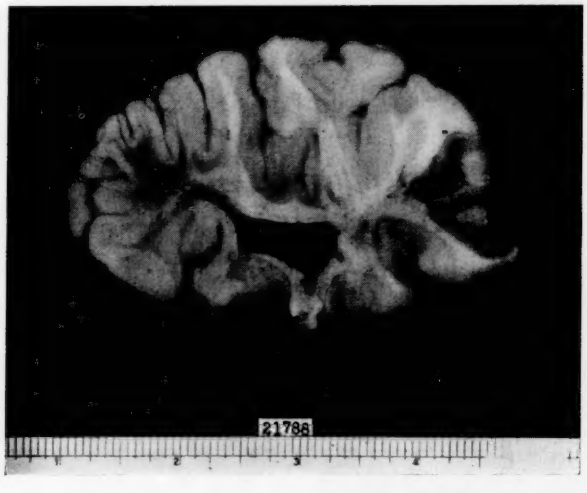


Fig. 24*B*.—In the brain nodules are demonstrated in the wall of the third ventricle.

VOL. 12 1960

Burghele, Joachim, and Goldstein described neurofibroma of the bladder leading to urinary symptoms in neurofibromatosis.

573. Srivastava and coauthors reported a case of *tuberous sclerosis* which had facial paresis, subungual fibromata, a retinal tumor, hemoptysis, and spontaneous remission of epilepsy as features of note. X-ray of the chest showed marked pulmonary reticulation. Chao reviewed the features of 8 childhood cases.

Mixed tumors of the viscera are familiar features of tuberous sclerosis. The case of Gutman and Leffkowitz is of interest because epileptiform seizures were found to be due to an islet cell tumor; the attacks were relieved by removal

Fig. 24*C*.—The white glycogen-containing tumors found in the myocardium are well demonstrated. A large tumor projected into the outflow tract of the right ventricle. It was probably responsible for the loud systolic murmur which had first been discovered at the left sternal border at the age of 2 weeks.

of the tumor. The clinical lesson of this report is that all epilepsy in patients with tuberous sclerosis should not be written off as part of the central nervous system involvement. (Fig. 23.)

Marshall, Saul, and Sachs reported 16 cases of tuberous sclerosis in two families. Neurosurgeons, they had their interest in these families aroused by the occurrence of brain tumor. In the first family the disease was known in three generations and ependymoma of the third ventricle was present in one case. In the second family at least four generations were affected. A mother and her 16-year-old son both had astrocytoma of the third ventricle. Harvey Cushing had removed the mother's brain tumor in 1932; in 1959 the patient was still

living without evidence of recurrence! The authors referred to the theory of Gunther and Penrose (J. Genet. 31:413, 1935) that there is a single major modifying gene determining severity of the disease:

E = epiloia (tuberous sclerosis); A = modifier (ameliorator)

EeAA—Normal but carrier of tuberous sclerosis
EeAa—Mildly affected by tuberous sclerosis
Eeaa—Severely affected by tuberous sclerosis

The authors concluded that the behavior of tuberous sclerosis in their two families was consistent with the Gunther-Penrose theory. (See Fig. 24.)

574. Pheochromocytoma occurs in association with *von Hippel-Lindau cerebelloretinal angiomatosis* (Chapman, Kemp, and Taliaferro). (See ¶507 for discussion of the association with neurofibromatosis.) One of Lindau's original patients had bilateral adrenal tumors at autopsy. Congenital cysts of the kidneys and pancreas also occur in association with the von Hippel-Lindau syndrome. The occurrence in the same individual of pheochromocytoma and evidences of *both* neurofibromatosis and von Hippel-Lindau disease is puzzling. One such case is reported by Chapman, Kemp, and Taliaferro. In a second case there seems to have occurred neurofibromatosis on the father's side and the von Hippel-Lindau syndrome on the mother's side; occurrence of both diseases in the proband's sibship was, therefore, probably coincidence. A family was reported by Bird and Mendelow.

Roizin and colleagues analyzed 12 cases of the *Sturge-Weber syndrome*, including study of 3 post mortem. The trigeminal involvement of the nevus flammeus may be bilateral and various parts of the trunk and extremities may be involved. Epilepsy, mental deficiency, and glaucoma are features. Calcifications are limited to cerebral tissue. No comment on familial occurrence was made. Furthermore, Chao in describing 8 cases made no mention of familial occurrence and in one of her cases an identical twin was normal. (Detailed zygosity studies were not described, however.) She likewise pointed out that the gyrate calcification seen in skull x-ray is located in the cerebral cortex, at a depth of 0.5 to 1.0 cm. from the meningeal surface.

575. From the Netherlands, van der Hoog described a case of *familial ataxia-telangiectasia* of the type described by Boder and Sedgwick (¶229). The 15-year-old girl had been hospitalized seven times for recurrent pulmonary infections. At the age of 7 years left lower lobectomy and lingulectomy had been performed for extensive bronchiectasis. Progressive cerebellar ataxia and typical conjunctival telangiectasia were present. Smith and Cogan described an 18-year-old Negro female with the same disorder; cerebrospinal fluid protein was increased and cerebellar atrophy was demonstrated by pneumoencephalogram. Siekert, Keith, and Dion described 2 siblings and a third unrelated child with ataxia-telangiectasia.

VOL. 12 1960

576. Spinocerebellar degenerations. In the sibship described by Stuart there was in addition to *Friedreich's ataxia*, epilepsy, adenoma sebaceum, multiple congenital anomalies with death in the first year of life, and the Laurence-Moon-Bardet-Biedl syndrome—in separate individuals, except that the latter syndrome occurred in one of the cases of Friedreich's ataxia. Coincidence seems likely. The parents were first cousins.

In 4 male siblings out of 6, cerebellar ataxia, progressive blindness, dilated pupils, and hyperactive deep tendon reflexes with clonus developed (Woodworth, Beckett, and Netsky). The autopsy findings were degenerative changes in the optic system and in the olivocerebellar, dorsal, and spinocerebellar tracts. The disease had its onset in adulthood in one, in adolescence in 2, and in childhood in one.

Hariga described hereditary spastic ataxia with chronic progressive ophthalmoplegia in 3 siblings and ophthalmoplegia alone in the son of one of the patients.

Brown stated that of 103 cases of "degenerative cerebellar ataxia" of all ages, 12 had a family history for the identical disorder. In 3 more there were other cases of pes cavus in the family. In 7 others an indeterminate neurological disorder existed in other members of the family but may have been unrelated.

Aagenaes described a family with 31 cases of *hereditary spastic paraplegia* in four generations. Prognosis for life was good. The inheritance appeared to be autosomal dominant. Histopathologic changes were found bilaterally in the lateral corticospinal tracts in the thoracic cord and in the fasciculus gracilis. In his review of the literature he pointed out that the disease is most often autosomal recessive but is dominant in 10 to 30 per cent of families. The classification of the hereditary spinocerebellar degenerations is in a confused state. The confusion is illustrated by the fact that in Aagenaes' family some members had ataxia in addition to spastic paraplegia.

Markson, Carnagham, and Young studied *hereditary cerebellar degeneration* in Light Sussex pullets. Clinically the disease was manifested by slight ataxia with fine tremors of the head and neck. The disease did not interfere with satisfactory egg laying. Histologically, degeneration of the cerebellar Purkinje cells and nerve cells of the granular layer was found. The disease behaved as a sex-linked recessive trait. Sex determination in birds is the opposite of that in man—the hen is the heterogametic sex ZW and the rooster ZZ. Only pullets (young hens) showed the disease. No affected males were observed from mating of the sons of affected females with affected females. The workers thought that either their experiment was too limited in numbers or the gene in homozygous state may be lethal.

577. Engel, Kurland, and Klatzo described two families with an inherited disease clinically indistinguishable from *amyotrophic lateral sclerosis.* In one family of Pennsylvania Dutch stock at least 11 members of four generations were affected by what was locally and popularly termed "Pecks' disease." In the second family 3 members of two generations were affected. Histopathologic studies revealed a consistent pattern of posterior column involvement.

578. Moretti and Staeffen reported *Crouzon's craniofacial dysostosis* and *syringomyelia* in a brother (aged 43) and sister (aged 60). They found two previous reports, one of a family, of syringomyelia with Crouzon's disease. Hydrocephalus has been described. The authors suggested that craniofacial dysostosis results "from compression of the prechordal mesoblast by exaggerated curvature of a neural tube which is abnormally long."

The paper of Dodge, Wood, and Kennedy reviewed experience with 5 cases of Crouzon's disease at the Mayo Clinic. Three were "familial," the disease having been known in three and four generations. In 2 cases syndactyly occurred in addition to the usual cranial synostotic malformation, prognathism and parrot nose, and exophthalmos with external strabismus; a similarity to Apert's acrocephalosyndactyly was suggested. In one case a fifth intracranial ventricle was demonstrated. Surgical palliative procedures were performed in 4 patients. Schiller also reported a large pedigree. Diagnosis from the family album is possible in this disease.

VOL. 12 1960

579. Feigin discussed *metachromatic leukoencephalopathy* from the point of view of histopathology and mechanism. As for the nature of the metachromatically staining material he stated: "These materials are presumably not mucopolysaccharides. Perhaps the only chemical information gained by demonstrating their metachromasia is that they are composed of large molecules with many anionic groups." He raised the possibility that it may "represent an abnormal intermediate in myelin formation."

Wohlwill, Bernstein, and Yakovlev described a form of leukodystrophy associated with megalobarencephaly (big head with large brain and no hydrocephalus). Other cases have been reported but this was the first report confirming its familial nature—4 in a sibship of 9 had "large heads" and died in infancy. The authors suggested that in accordance with Hallervorden's classification this is a dysmyelinogenic leukodystrophy; that is, the defect concerns the formation of normal myelin sheaths and not degeneration of myelin as in the myelinoclastic leukodystrophic conditions.

Lichtenstein and Rosenbluth described 2 unrelated boys with leukodystrophy (called merely "Schilder's disease" by them) in which there was melanoderma. At autopsy in one, no adrenal tissue could be found. Therefore, the cutaneous pigmentation was presumed to be Addisonian.

580. Brodal and Hauglie-Hanssen discussed the clinical and pathologic features of 2 cases of the *Dandy-Walker syndrome*—congenital hydrocephalus with defective development of the cerebellar vermis. In mice what may be the same syndrome occurs due to a monohybrid recessive gene. The chief anatomic finding, apart from generalized hydrocephalus, was underdeveloped vermis which was continuous posteriorly with a membrane which, made up of ependyma and connective tissue, appeared to represent the extremely enlarged roof of the fourth ventricle. Considering the fact that the foramina in one case were patent and considering the pathologic findings in the mice, the authors concluded that the atresia of the foramina cannot be considered a primary factor in the anomaly.

581. Daly and Yoss studied a family with 12 instances of *narcolepsy* and 3 other possible cases in three generations. The pedigree pattern is consistent with autosomal dominant inheritance. Whereas about two-thirds of all cases of narcolepsy (sleeping attacks) are associated with cataplexy (paroxysmal attacks of weakness or frank paralysis, associated especially with strong emotion), only one-third of the affected persons in this family displayed cataplexy. Furthermore, in these 3 the weakness was mild. Treatment with Ritalin seems to be effective (Yoss and Daly).

582. To get a more representative evaluation of mean age of onset in *Huntington's chorea*, Wendt, Landzettel, and Unterreiner examined data on 762 patients born between 1870 and 1899. The mean ages of onset for males and females, 44.25 and 43.69 years, respectively, were not significantly different but were different from the figures of Panse (1942), who in a study of 459 cases arrived at a mean age of onset of 36.67 years. Use of patients born in the period closer to the time of the investigation is likely to weight the figures with cases of earlier onset.

Reed and Neel, in a survey of all cases of Huntington's chorea identified in the lower peninsula of Michigan, found that the relative reproductive fitness of choreic individuals when compared with their nonchoreic siblings is about 1.12 ± 0.12, whereas the relative fitness of heterozygotes (i.e., overt choreic persons plus individuals heterozygous for the gene but thus far without chorea) was about 1.01 ± 0.11 when compared with homozygous normal siblings. The unexpressed heterozygous state was identified by the fact that a choreic offspring had been produced. There was a significantly lower fertility in nonchoreic siblings than in the general population, 0.77 ± 0.08. The same workers examined the question of mutation in 196 kindreds. No specific instance of mutation could be definitely identified because nonpenetrance could not be definitely excluded. However, in only eight kindreds were both parents of a single patient with Huntington's chorea found to be (1) 60 years of age or older and (2) normal.

583. Epilepsy. Friedlander discussed the hereditary pattern of "cerebral light sensitivity" (photogenic epilepsy). Daly, Siekert, and Burke had a family in which 3 of 4 siblings had mental retardation, spastic diplegia, and epilepsy precipitated by flashing lights. Eisner, Pauli, and Livingston studied 669 epileptic individuals and 3,362 close relatives, in comparison with 470 controls with 2,856 of their close relatives. A small but significant familial aggregation was found for idiopathic major motor epilepsy. The highest empirical risk was for relatives of probands with major epilepsy starting before 3½ years of age. Of such relatives 9.4 per cent had epilepsy by age 39½ years as compared with 2.3 per cent in the controls.

584. Zeman, Kaeilbing, and Pasamanick studied a family in which 12 individuals were affected by *dystonia musculorum deformans* (torsion dystonia). They found in the literature reports of twenty-nine families with more than one case. A review of these, together with their own pedigree, led to the conclusion

that the disease is usually transmitted as an autosomal dominant trait "although a recessive mode of inheritance may exist." We have had an opportunity to observe a father, son, and daughter with dystonia musculorum deformans. The peculiar posturing, especially holding of the left arm behind the head, suggested hysteria in early stage of investigation. Cooper reported good results from chemopallidectomy in this condition.

585. Aronson, Aronson, and Volk analyzed genetically 131 cases of *infantile amaurotic idiocy.* A large majority were of Jewish descent. Consanguinity was frequent. A recessive mode of inheritance with full penetrance fitted the data.

Forsythe, McKeown, and Neill reported on 3 males with Niemann-Pick's disease still alive at 19, 19, and 10 years of age.

586. Wheelan described a family in which the mother and 5 of 10 children had the *Alzheimer type of presenile dementia.* Multiple blood groupings were performed by Race in 31 members of the family. A linkage between the "Alzheimer locus" and the MNSs locus was suggested; Race cautioned, however, that the segregation might be due to chance.

Schenk followed up on a family with Pick's disease (lobar atrophy) originally studied in 1938, at which time 10 cases were identified in the family. Ten further cases were found. The pedigree suggests autosomal dominant inheritance. Swain concluded that the electroencephalogram is useful in detecting early Alzheimer's disease but is useless in Pick's disease.

Mental defect: 587. Goodman and Herndon provided a useful review of genetic factors in mental retardation.

At the Pacific State Hospital, Pomona, California, Wright, Tarjan, and Eyer made observations on those families in which at least 2 siblings had mental defect. The objective was to narrow down the group which would be intensively investigated for evidence of a specific biochemical defect. Sixty-one such families were found. Among these, four had phenylketonuria, one Hurler's syndrome, one ectodermal dysplasia, one true microcephaly, one congenital cataracts, one the Roussy-Lévy type of spinocerebellar degeneration, and two Mongolism. Report of biochemical studies on the remaining sibling groups is promised as a later report.

588. Van den Bosch attempted total ascertainment of *microcephaly* in the Netherlands. Although he had anticipated that patients over the age of 10 years would be readily identified because of institutionalization, this proved not to be the case. Female microcephalic individuals, as is true for mental defect in general, were not represented in his series in the expected ratio. Van den Bosch separates a genetic variety of microcephaly manifested by multiple cases in the family, frequent parental consanguinity, absence of neurological defect and skeletal or other malformation (except, of course, that of the skull), and preservation of a well-integrated, extrovert personality. The incidence of "special genetic microcephaly" was estimated at about one in 250,000 in the Netherlands, of all micro-

cephaly about one in 93,000. The data were consistent with autosomal recessive inheritance. The genetics of microcephaly was also discussed by Koch. Brandon, Kirman, and Williams observed microcephaly in one of monozygous twins. The blood groupings probably corroborate monozygosity.

589. Blumel and Kniker reported 5 new patients with the *Laurence-Moon-Bardet-Biedl syndrome*, of whom 3 were in one sibship. They also reviewed the cases in thirty-four publications which have appeared in the English literature since the review of Burn in 1949. The variability in expression of the syndrome was noteworthy. On the basis of 65 cases the authors placed the incidence of five features at the following levels: obesity, 83 per cent; mental deficiency, 80 per cent; polydactyly, 75 per cent; retinitis pigmentosa, 68 per cent; genital dystrophy, 60 per cent; and other cases in the family, 48 per cent. The syndrome was thought to be inherited as an autosomal recessive trait. The authors stated that the most convincing single pedigree supporting this genetic hypothesis is that of Kalbian (J. Clin. Endocrinol. 16:1622, 1956). They described the autopsy findings in one case. There were pulmonary stenosis and ventricular septal defect (a sibling with the syndrome was thought also to have congenital heart disease) and almost complete absence of the corpus callosum. (See ¶'s 543, 554.)

OL.
12
960

590. Blassingille described from New England 2 cases of mental retardation, congenital skin disorder, and congenital spastic disorder. The family history in one case revealed multiple disorders suggesting that the proband's disease was genetic but of complicated nature. The relationship to the *Sjögren-Larsson syndrome* (congenital spastic disorder, congenital ichthyosis, and oligophrenia) is uncertain.

591. Mongolism. Certainly the most important development with reference to this syndrome and one of the most important in all medical genetics in 1959 was the demonstration that the probable "cause" of Mongolism is the trisomic state resulting from the presence of an additional acrocentric (subterminal) autosomal chromosome, making a total count of 47 (¶381). Presumably nondisjunction during parental (probably maternal) gametogenesis is responsible. The increase in nondisjunction in aging Drosophila females (Mottram, J. Exper. Biol. 7:370, 1930) may have its counterpart in Mongolism in man, thereby explaining the maternal age effect. A gene for nondisjunction is known in Drosophila. Such a gene, if present in man, might have a pleiotropic effect to account for the dermatoglyphic peculiarities in otherwise normal relatives of Mongolian idiots. The 100 per cent concordance of monozygotic twins would be expected. Mongoloid individuals are said (Jacobs and associates) to resemble the mother antigenically more than the father.

Ek found a tendency to hyperthyroidism in the mothers of Mongoloid infants. The mean protein-bound iodine in 41 mothers was 7.1 μg per 100 c.c. as opposed to a normal of 5.9 μg per 100 c.c. in other women of the same age. In 12 of the 41 the thyroid was pathologically palpable and 2 had had thyroidectomy. Even if the "cause" of Mongolism has been satisfactorily identified as a chromo-

somal aberration, studies of the mother must continue in order to determine possible "causes for the cause"—why does nondisjunction occur? Furthermore, continuing studies of the metabolism and other features of affected offspring can be of academic significance in defining the effect of the trisomic state which Mongolism apparently represents. Studies of the latter type were reported by Runge, who found relative hypoglycemia and abnormal glucose tolerance tests in 30 per cent under 10 years of age and in 99 per cent over 40 years of age.

Berg, Brandon, and Kirman found a greater response to atropine in Mongolian idiots than in other mentally defective persons matched for age and sex. Sensitivity to atropine was measured by the rapidity of dilatation of the pupil and the duration of the dilatation after instillation of one drop of atropine one per cent in the eye. Hypersensitivity to atropine in Mongolism has long been mentioned in clinical teaching at the Johns Hopkins Hospital. This is apparently the first careful study of the matter.

The teeth in Mongolism were studied by Hertel and Zanalda, and the congenital heart disease by Powell and by Liu and Corlett. Gibson and Frank described two sibships, each with 2 cases of Mongolism.

In a Cabot C.P.C. case, carcinoma of the stomach occurred in a 17-year-old male with Mongolism. The increase in acute leukemia in Mongolism is probably well established (Krivit and Good, A.M.A. J. Dis. Child. 94:289, 1957). The frequency of other malignancies has, seemingly, not been studied.

Miscellaneous: 592. Bennett, Rhodes, and Robson reported on ***kuru*** ("the shakes"), a rapidly progressive neurological disease of the Fore natives of New Guinea. The initial pathologic change is probably cerebellar (Simpson, Lander, and Robson). The disease is responsible for about one-half of deaths in Fore females and one-tenth of deaths in Fore males. Whereas the age of onset seems to be unimodal in males, with a mean of about 14 years, the female distribution is bimodal with one mode at about 8 and the other at about 33 years. A genetic hypothesis is advanced that affected males are KK and affected females are either KK (early onset) or Kk (late onset). The authors also indicate that the childhood death rate of the offspring of women who die of kuru is higher than average. If a preponderance of males exists in this group of infants and if the cause of death is related to kuru, then an alternative hypothesis would be that both the KK and the Kk forms of the disease occur in males and that the disease is, in fact, milder in females with delay of the two modal ages of onset. The frequency of gene K was estimated to be 37 per cent and the frequencies of the three genotypes, KK, Kk, and kk, to be 14, 47, and 39 per cent, respectively. Collection of reliable pedigree data is difficult in this population. (See also Gajdusek and Zigas.)

593. Ross described mother and daughter with *intracranial "berry" aneurysm.* The daughter also had two angiomatous malformations of cerebral vessels. Edström, Grontoft, and Sandring reported on *Refsum's disease* (retinitis pigmentosa with hemeralopia, hypertrophic polyneuritis, cerebellar ataxia, high cerebrospinal fluid protein, and electrocardiographic changes) in 3 siblings, with one autopsy. (See ¶235.)

594. A study of *multiple sclerosis* in twins and their relatives lends support to a genetic factor (among several) in the etiology of the disorder (Mackay and Myrianthropoulos).

595. Vogel and Götze and also Vogel and Helmbold published articles based on the studies of the genetics of the normal *electroencephalogram* conducted by Vogel and his colleagues in recent years.

596. Psychiatric disorders. Kallmann gave a general review.

Rosenthal reasoned that both genetic and nongenetic factors in *schizophrenia* probably exist and that the nongenetic factors should be especially prominent in those schizophrenic monozygotic twins who have a normal cotwin. Analyzing the twin data of Slater from this point of view, he found that a positive family history for schizophrenia was almost totally absent in the discordant group and present in about 60 per cent of the concordant group. The concordant cases were most often catatonic; the discordant cases tended to be paranoid. At least among males, the concordant cases tended to have poorer premorbid adjustment. He concluded that environmental factors are more important, and genetic factors less important, in paranoid schizophrenia than in catatonic schizophrenia.

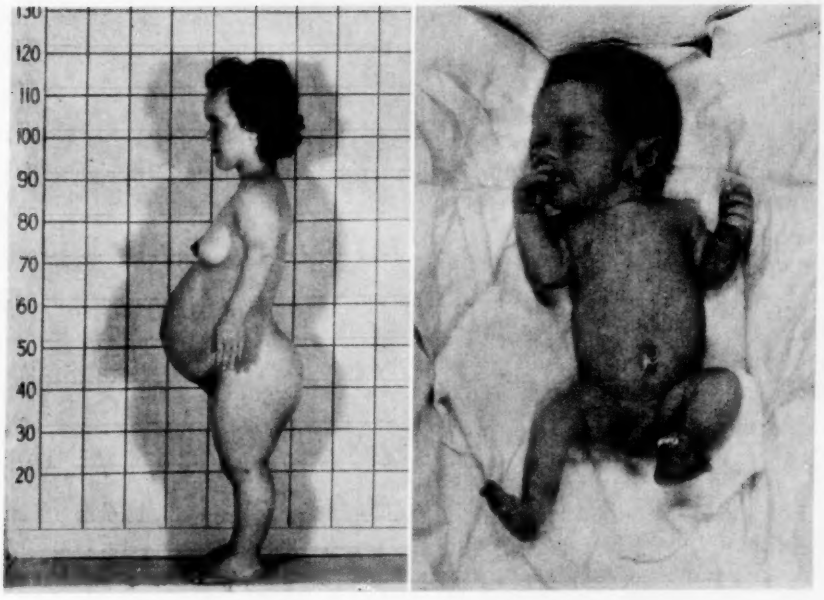
McConaghy performed an objective sorting test on both parents of 10 schizophrenic patients, and on at least one parent of all patients he found scores characteristic of schizophrenics. The probability that the parents came from the same population as the controls was less than 0.1 per cent ($p < 0.001$).

Malamud stated that the condition which is most likely to be confused with childhood schizophrenia is Heller's disease, in which, beginning with a character disorder at about 3 or 4 years, there is slow mental regression followed by motor disturbances, possibly speech loss, and finally idiocy. The pathologic change consists of "diffuse lipoid degeneration of the ganglion cells." He described three pairs of affected siblings. Errors of diagnosis are likely to result from failure to recognize the neurological signs.

XX. SKELETAL SYSTEM

597. In a long review, Grebe discussed hereditary dwarfism under the following headings *inter alia:*

Proportionate dwarfism
Chondrodysplasia
Osteogenesis imperfecta
The Ellis-van Creveld syndrome
Chondrodystrophia calcificans congenita
Multiple cartilaginous exostoses
Arachnodactyly
Acrocephalosyndactyly
Cleidocranial dysostosis
Renal rickets



A. *B.*

Fig. 25*A* and 25*B*—Achondroplastic dwarfism in three generations. *A*, N. M. (J.H.H. 716735) is 24 years old (II 3). Note that the shortening of the extremities is more pronounced proximally than distally. The patient was pregnant at this time. Compare Fig. 15*A* (Ellis-van Creveld syndrome), in which distal shortening is more striking. *B*, Photograph of newborn first offspring (III 1) of patient shown in *A*. Measurements are unreliable indices of achondroplasia at this stage; however, the x-ray changes in the pelvis are pathognomonic.

598. *Achondroplasia* in dogs seems to be radiologically, pathologically, and biochemically identical to the disease in man and in cattle and rabbits (Gardner). The disease in dogs, unlike that in man, is inherited as a recessive trait. Case reports were provided by Zanchi; his second case would seem, however, to be one of osteogenesis imperfecta, not achondroplasia. Meeuwisse treated 3 achondroplastic infants with pituitary growth hormone (STH) without effect. (Fig. 25.)

Takahashi reported on a large experience with achondroplasia (chondrodystrophia fetalis) and with a heterogeneous group which he calls chondroosteodystrophy and which includes the Morquio syndrome and at least three other entities according to the classification proposed by the author.

Neel and Schull estimated the frequency of sporadic cases of the achondroplastic phenotype in 69,464 births in three Japanese cities to be 24.5×10^{-5}. The births were from parents who had not received significant amounts of radiation. Furthermore they presented evidence for the mixed etiology of achondroplasia and the inadvisability of basing estimates of mutation rate on the frequency of sporadic cases of the achondroplastic phenotype.

599. Maroteaux and Lamy pointed out that all cases labeled "Morquio's disease" do not involve the same disease. There are differences especially in the

VOL. 12 1960

extent of involvement of the extremities and in the degree to which growth is retarded. They reported 3 cases in which the growth of the extremities was so retarded that achondroplasia was simulated; hence, their title, "the pseudo-achondroplastic forms of the spondylo-epiphyseal dysplasias." The features differing from those of classic achondroplasia included later clinical onset, greater involvement of the hands, and characteristic changes in the vertebrae and epiphyses.

Lomas and Boyle described cases of osteochondrodystrophy in three successive generations and labeled the disease "the Morquio syndrome." Wise and Carter pointed out that Lomas' suggestion that the trait was autosomal recessive in this family is unlikely and that it is also unlikely that the entity is the same as

C.

D.

Figs. 25*C* and 25*D*.—Facies and hands of second offspring (III 2) of patient shown in *A*. This child, 16 months old at the time of study, is also affected.

that described by Brailsford and Morquio. In Lomas' family the disease resembled more that described by Jacobsen (J.A.M.A. 113:121, 1939). On the other hand, Maudsley thought it might be multiple epiphyseal dysplasia. The report serves to emphasize the confused state of the nosology of osteochondrodystrophies.

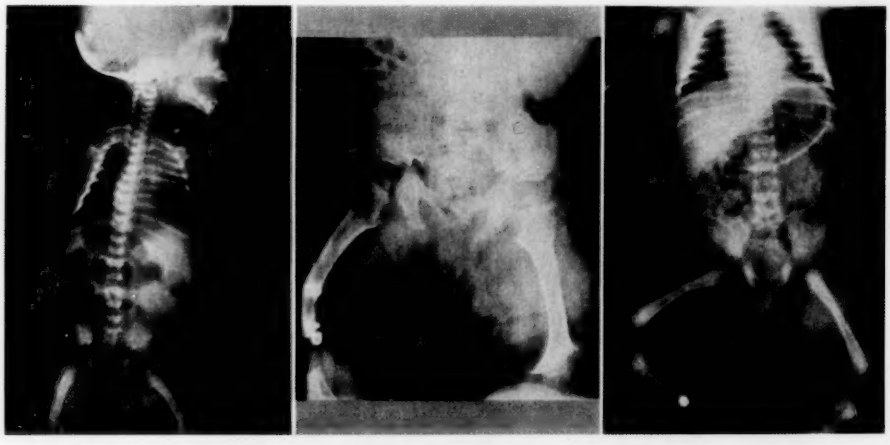
600. Elsbach described an autosomal dominant form of *epiphyseal dysplasia* which involves mainly the proximal epiphysis of the femur and is called by him microepiphyseal dysplasia because of the small size of the affected epiphyses.

Ödman described hereditary epiphyseal dysostosis in members of three generations of a family.

601. Margolis described a 48-year-old barber with *Ollier's disease*—enchondromatosis. As in Ollier's cases the disease was unilateral, affecting both extremities on the left. The family history was negative. No statement is made about children of the proband. Unlike multiple exostoses, or diaphysial aclasia, which displays a striking genetic background, none seems to be present in Ollier's disease. Examination of the chromosomes might be productive.

602. Welford observed facial paralysis in association with *osteopetrosis*, in an 11-year-old boy. Thirteen other male members of five generations of the family were affected. All persons affected by osteopetrosis showed involvement of the facial nerve which usually had its onset at about the age of 12 years.

603. Noack described *acrocephalosyndactyly* in a 43-year-old man and his only child, aged 11 weeks. Craniostenosis, tower-skull, synostosis, and syndactyly were present in both. Kluge described a case of acrocephalosyndactyly (Apert's



E. *F.* *G.*

Fig. 25*E*, 25*F*, and 25*G*.—Shown here are x-rays of the 3 offspring of the patient shown in *A*. Two (*E* and *F*) show achondroplastic dwarfism; the other (*G*) is normal. Two of the x-rays (*E* and *G*) were taken in the neonatal period; the patient was 16 months old at the time of the view shown in *F*. The typical x-ray changes shown in *D* and *E* permit definitive diagnosis (¶253); the ilium is shortened. The greater sciatic notches are reduced to narrow, deep clefts. In the lumbar spine excessive cartilage is shown by the wide intervertebral spaces. The lumbar vertebrae taper downward.

syndrome). The parents were unrelated but the mother was 44 and the father 56. Because of a contracted pelvis both of two deliveries were by cesarean section. There had been a miscarriage between the birth of this and of a previously normal child. Apart from deformity of the head and extremities and mental retardation, the child was healthy. Features were IQ of 50, cranium seemingly flattened anteroposteriorly with expansion of the skull sideways and upward, marked hypoteleorism, "anti-Mongolian" slant to the eyes, rudimentary cleft palate, webbing and fusing of digits, and "copper-beating" of the inner plate of the calvarium by x-ray. Gordon described 37 cases of *craniostenosis* in South Africans. He was of the opinion that this is a condition distinct from both

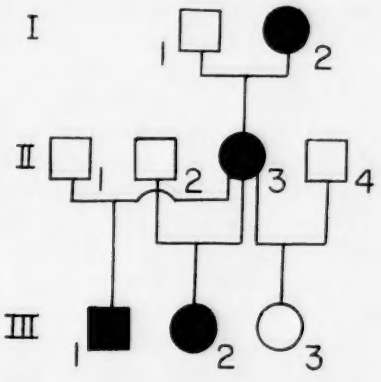


Fig. 25*H*.—Pedigree. The fact that each of the 3 children in the third generation had a different father, each with a normal skeleton, strengthens the hypothesis of dominant inheritance.

Crouzon's craniofacial dysostosis (¶578) and Apert's acrocephalosyndactyly. Of nine families studied in detail five had multiple cases. The condition seemed to be more frequent in males.

604. Steinberg, Steinberg, and Steinberg reported 3 cases of *cleidocranial dysostosis* in one family. They referred to the medicolegal case in which an adult with this disorder made a practice of getting caught in revolving doors and then suing for alleged fracture of the clavicle with malunion.

605. Thompson described "cherubism" (*familial fibrous dysplasia of the jaws*) beginning at about 2 years and still progressing at 8 years in a boy. The disfiguring enlargement of the lower face and jaw was exaggerated by bilateral smooth enlargement of the submandibular lymph nodes. X-ray revealed multilocular cystic disease of both jaws and also cystic change in the anterior ends of all ribs bilaterally. The maternal grandmother was noted to have had swelling of the lower face at the age of 3 to 4 years, progressing steadily to the age of 20 years. Jones in 1933 described the disease in 3 siblings. Choremis and colleagues wrote on familial multilocular cystic disease of the jaws, apparently the same as cherubism.

606. Lother found a *parietal foramen* (foramina parietalia permagna) by x-ray of the skull in 3 brothers in a sibship of 5 and in the daughter of one and the son of another—5 cases in two generations. Hyperteleorism was associated.

607. Otto Schales, Professor of Biochemistry at Tulane University School of Medicine, has made a thoroughgoing study of *congenital hip dysplasia* (congenital dislocation of the hip) in German Shepherd dogs. The clinical characteristics are precisely like those in man. The incidence of radiologic abnormality of the acetabulum (he recognizes four grades) is much higher than the incidence of frank dislocation of the hip. Schales quotes the French surgeon Calot (1920) as comparing the normal acetabulum to half an orange and the dysplastic acetabulum to half a lemon cut lengthwise. Schales' articles are useful reading as indications of the problems one encounters in dealings with breeders and some veterinarians when one wishes to investigate a disease trait in domestic animals. The means for eliminating the gene from the German Shepherd are readily available. On the contrary, the gene has been bred for selectively in recent years because of a show ring impression that the most beautiful dogs were those which stood with the rear legs projecting far behind. Schales points out that this stance is a symptom of unstable hip! "I would say that probably as many as 75 per cent of all German Shepherds have hip dysplasia." He is satisfied that it is inherited as an autosomal dominant trait with irregular manifestation, which is also the leading contender for the mode of inheritance in man although this view has been challenged (¶261). The disease is known to affect at least thirty-seven different pure breeds of dog. Reports by veterinarians (Schnelle; Snavely; Henricson and Olsson) indicate their awakening interest in the subject. That of Snavely suggests that the genetics is complicated as in man. The existence of an animal analogue may be helpful in unraveling the genetics of the disease in man.

Geiser and Buri in 236 pairs of twins, at least one of which was affected by congenital dislocation of the hip, reported 42.7 per cent concordance in monozygotic twins and 2.8 per cent in dizygotic twins.

608. Howarth in discussing *coxa plana* said that "no definite hereditary or familial relationship has been found"—an incorrect statement. Wausbrough and associates concluded that coxa plana (Legg-Calvé-Perthes disease) is inherited as a sex-influenced autosomal dominant trait. Among siblings born subsequent to 124 probands, one in 35 was affected as compared with one in 20,000 in the general population. Among 129 cases there were 105 males and 24 females. In 23 there was bilateral involvement; both of a pair of monozygotic twins were affected; 12 had relatives with proved coxa plana; and 7 more had relatives with undiagnosed limp or hip trouble.

609. Champion and Cregan reported on 2 siblings, girl and boy, born with a marked *popliteal webbing* resulting in the knees being held flexed at an angle of 100 degrees. Both had in addition deformity of the mouth (cleft soft palate, sinuses of the mucous membranes of the lower lip) and either missing or syndactylous toes.

VOL
12
196

610. In 1868 Friedreich described 2 brothers by the name of Hagner, 26 and 22 years of age, with generalized skeletal hyperostosis. Their hands and feet were clumsy and the forearms and lower legs thickened, in part from the periosteal overgrowth of the long bones, in part from changes in the skin. Postmortem findings were reported in the elder brother by Arnold (1891). When he described acromegaly in 1886 Marie thought the Hagner brothers had this condition. When Bamberger (1889) and Marie (1890) described hypertrophic pulmonary osteoarthropathy, Marie changed to the view that the Hagners had the latter condition. However, there had been no cardiac or pulmonary symptoms. Tornblöm has now collected three sibships with 2 brothers, 2 brothers, and 3 brothers, respectively, affected. The fingers are clubbed. Affected males do not have children. The patients exhibit hyponatremia with maintained urinary excretion of sodium. There is no clear evidence of either adrenal or renal defect.

OL.
12
960

611. In Brazil Freire-Maia, Zuelce-Salgado, and Amundsen Koehler studied a family with "*congenital amputations*" and other hereditary bone aplasias and hypoplasias of the upper extremities. In connection with most of the reported pedigrees, dominant inheritance has been suggested; however, there are some suggesting recessive inheritance. The authors describe a family of the latter type. For a recessive trait, expressivity was extraordinarily variable. For example one patient has hypoplasia of the clavicles and scapulae, absence of the entire left upper extremity, and an exceedingly diminutive remnant of the right upper extremity. Two of three marriages resulting in defectives were consanguineous. Two affected persons had a total of 14 normal children and no affected children. The only amputee who had an affected child was married to a niece. There was no evidence of reduced viability or reduced fertility of affected persons.

612. Robins described an autosomal recessive mutation causing clubfoot in the mouse.

613. Khosrovani reported *ectrodactyly* ("lobster claw") in five successive generations with a total of 25 affected persons (13 men and 12 women). In 8 of 19 examined persons, the condition was unilateral. The inheritance was apparently irregularly dominant with wide expressivity. His pedigree contained 2 presumably phenotypic normal "conducteurs," one of whom was personally examined. No note is made of whether x-rays of the hands and feet were taken in this case. Blood group and PTC data were collected, as well as observations on a variety of morphologic traits.

XXI. SKIN AND OTHER INTEGUMENTAL STRUCTURES

614. A useful classification and list of genodermatoses (genetically determined skin disorders) was provided by Bloom. He refers to work of Ruiter (1953 and 1954) suggesting that there is a metabolic defect of lipid of blood vessels involved in the pathogenesis of *angiokeratoma corporis diffusum universale* of Fabry. Karr described a case of Fabry's disease in a 33-year-old Latin

American man. All cases in the literature have been in men. The trait may well be sex-linked recessive (or intermediate, since there is a suspicion in one report [¶281] of involvement in the mother of an affected male).

615. Curth and Aschner recognized three forms of *acanthosis nigricans:* (1) benign, (2) malignant, and (3) pseudo. In all 26 persons with malignant acanthosis nigricans—secondary to visceral carcinoma—no other cases were found in the family. They state that benign acanthosis nigricans is inherited as a Mendelian dominant trait. Nine of 13 families had multiple cases—27 in all, 14 male and 13 female. Three generations of one family and two of two others were affected. Irregularities in the presumed dominant inheritance were indicated by the description of multiple affected siblings with normal parents. Only the index case was found in the families of 26 patients with "malignant" acanthosis nigricans, that is, associated with visceral malignancy.

616. Haber wrote on *Miescher's elastoma* (elastoma intrapapillare perforans verruciforme). The lesions occur especially on the neck. They begin as conical or flat-topped, grayish yellow or pink papules 2 to 3 mm. in diameter and height. There is likely to be a hyperkeratotic plug and secondary inflammation may occur. Histologically, an agglomeration and degeneration of elastic fibers is seen with an extrusion of the balled-up elastic fibers into the epidermis. A matter of great interest are the facts that Avery (1958) saw the condition in a young man who died of dissecting aneurysm, Storck (1952) saw it in a case of Marfan's syndrome, and Meara described it in the Ehlers-Danlos syndrome.

Hitch and Lung described what they believe are the first cases of Miescher's elastoma reported in the United States. They consider a better designation to be "elastosis perforans serpiginosa." Most cases are in men. Among their 5 patients there was one with blue sclerae and a second who had had multiple "pathologic bone fractures" as had also his father! We have, therefore, suggestive evidence that Miescher's elastoma can occur with three heritable disorders of connective tissue: Marfan's syndrome, the Ehlers-Danlos syndrome, and osteogenesis imperfecta.

617. Klunker followed up a family affected by *epidermolysis bullosa simplex* (Köbner) which was first reported in 1892. The total number of affected generations numbered seven and of affected persons 28 (19 men and 9 women). Inheritance as a dominant trait was confirmed.

618. Loewenthal presented evidence that pyogenic bacteria play a role in *familial benign chronic pemphigus.* This disease is, in his view, a manifestation of pyoderma (impetigo circinata) in persons with inherited predisposition to acantholysis. Raaschov-Nielsen discussed the genetics of this disorder.

619. Loewenthal assigned the name "albinoidism" to a hereditary condition characterized by a white "blaze" in the scalp hair and/or patches of leukoderma. Epitheliomata occur with increased frequency. White forelock is also

seen (1) in the Waardenburg syndrome (¶528), which is inherited as an autosomal dominant trait and in which patches of leukoderma also occur and (2) as simple white forelock inherited as an autosomal dominant, as a sex-linked recessive, or as an autosomal trait dominant in males and recessive in females (Gates, *Human Genetics*, 1946).

620. In reviewing the subject of *psoriasis*, a common disorder in which familial aggregation is clear, Downing quotes Shelley and Arthur (1958) as stating that the basic defect seems to concern enzyme systems involved in the protein metabolism of the epidermis. Keratinization specifically may be defective. The sulfhydryl content of psoriatic scale is very high. Pentose levels in psoriatic scale are three to ten times normal.

621. Kooij and Venter reported on a familial disorder: *atrophodermia vermiculata* with unusual localization and associated congenital anomalies. On the face there were symmetric, small, crowded areas of skin atrophy. The congenital anomalies included congenital heart block, coarctation of the aorta, Mongoloid facies, and slight oligophrenia.

622. Stevanovic described a family in which *alopecia congenita* was inherited as an autosomal incomplete dominant trait with varying expressivity and associated with hyperkeratosis of the palms and soles. The fingernails showed mild dystrophic change. In a female child the scalp hair was unaffected but the eyelashes and eyebrows were absent and keratoderma and onychodystrophy were displayed.

Lubowe described two families with multiple cases of alopecia areata: 3 brothers were affected in one family, the mother and a daughter and a son in the other.

623. Stephens and Isaacson observed 17 cases of *multiple subcutaneous lipomatosis* in three generations. Usually the condition does not become evident until the age of about 35 years, although in one subject lipomata were present at age 9. In none did malignancy occur. Inheritance may be autosomal dominant.

624. Vacca, Knight, and Broun concluded from a study of 51 persons with *xanthelasma* that there are several types of disturbed lipid metabolism which can be so expressed.

625. Mohler described cases of *hereditary ectodermal dysplasia* of the anhidrotic type. Saddle nose and primary hypogonadism were features not previously described. In the previously reported families the inheritance has most often been that of a sex-linked recessive trait.

XXII. TEETH

626. Chaudhry discussed *hereditary enamel dysplasia* (amelogenesis imperfecta) and described five families, each with many affected members. The pattern of inheritance seemed to be autosomal dominant. The defect is primarily

ectodermal although the exposed dentine may become secondarily changed. Toller reported 6 cases. Johnson described three families with *dentinogenesis imperfecta* containing at least 62 affected persons. The disorder is also autosomal dominant and can be associated with osteogenesis imperfecta.

627. Goodman and colleagues compared *dental caries*, bacterial flora of the mouth, and salivary characteristics in twins of like sex of monozygotic and dizygotic types. The mean interpair variation of the caries experience ratio (ratio of decayed surfaces to surfaces available for decay) of dizygotic twins exceeded that of monozygotic twins. Evidence of heritability of the pattern of mouth flora and salivary characteristics was obtained.

In mice Baer and Liekerman demonstrated strain differences in susceptibility to periodontal disease from dietary deficiencies and changes in the physical consistency of diet.

VOL. 12 1960

628. In Japan Saito reported a genetic study of *anomalies of the deciduous teeth* in 7,589 infants, 2,740 older children, and 141 families including at least one child with abnormal deciduous teeth. A proportion of those with abnormal deciduous teeth were later examined for abnormalities of permanent teeth. Data were also provided on the frequency of fusion and/or absence of deciduous teeth, peg-shaped teeth, preconical or conical incisors, and supernumerary median teeth. In the family studies relatives of probands were found to have teeth anomalies at a higher rate than did the general population. It is fair to state that the segregation ratios obtained from different types of matings indicate some complexity in the genetics. A seemingly useful review of the limited literature on genetic control of dental variations is provided.

XXIII. URINARY SYSTEM

629. Defects in renal tubular function are discussed elsewhere (e.g., ¶400). Lowe's syndrome (¶197) is such a condition. Schoen described 2 siblings, dizygotic twins, with the Lowe-Terry-McLachlan syndrome (abnormal renal excretion of ammonia, hydrogen ions, phosphate, and amino acids, cataracts, glaucoma, and retarded growth). An abnormality of the mitochondria of the renal tubules was demonstrated in both cases. The author came to the following curious conclusion: "The fact that the patients are double ovum twins with no history of similar disorders in 3 generations of the family speaks against a hereditary basis for the syndrome."

630. Four of 7 siblings were affected by *cystic disease of the liver and kidney* in a family reported by Lathrop. Both parents were thought to be unaffected. Symptoms, more often renal than hepatic, began in childhood; 2 children developed portal hypertension. This disorder is clearly distinct from, and much rarer than, the common variety of cystic disease of the kidneys which usually does not become clinically evident until adulthood, is transmitted as an autosomal dominant trait, and is rarely accompanied by cystic change in other organs. In

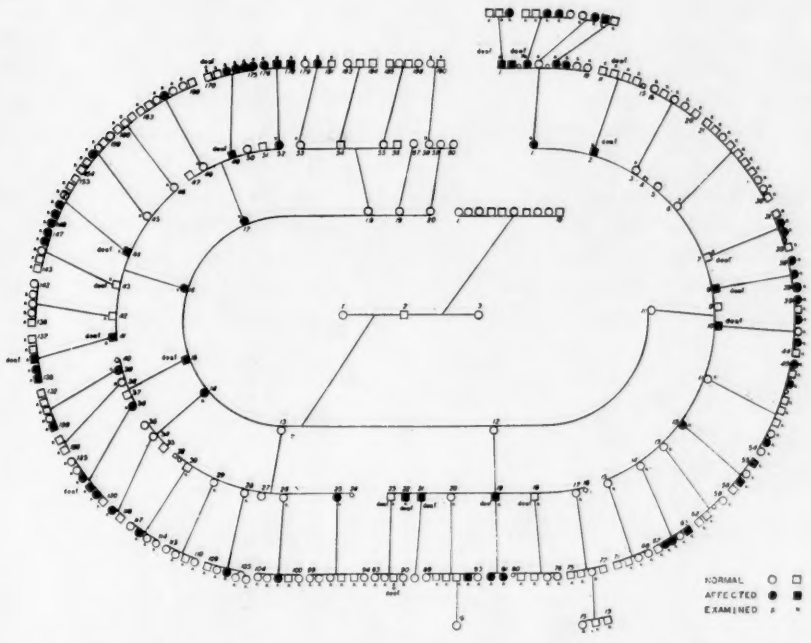


Fig. 26.—The Utah pedigree of hereditary nephritis. (From Perkoff and Coauthors: Arch. Int. Med. 102:733, 1958.)

his monograph on cystic disease of the kidney, Dalgaard (1957) concluded that there is a congenital form, possibly inherited recessively, distinct from the common variety.

Ward, Haltiwanger, and King found a low renal threshold for glucose in a case of polycystic kidney disease. There was no glycosuria during fasting.

631. Goldman and Haberfelde described a kindred in which 6 males had died of uremia, 5 had clinical glomerulonephritis, and 5 had intermittent albuminuria.

Russell and Smith described a brother and sister with "hereditary hematuria." One maternal uncle died of uremia at the age of 40 years; another had asymptomatic hematuria (age 28 years). The report is confusing because of the use of square symbols for females and round symbols for males in the pedigree chart. The authors' conclusion, "The abnormality appears to be genetically transmitted as a dominant trait," may be correct but is probably not justified by the available information in this family.

As indicated in ¶282, Perkoff and associates had suggested that hereditary nephritis may be a partial sex-linked dominant trait in a large Mormon pedigree on which they reported (Fig. 26). Graham offered an alternative genetic hypothesis based on the fact that there is a significant deficiency of males in the entire kindred, especially among the offspring of affected fathers and affected mothers in generation III. His proposal is that the trait is an autosomal dominant which

is sex influenced to the extent that many affected males "are never seen, presumably because of death *in utero*." An appealing feature of this hypothesis—and of the alternative suggested by Morton—is its consistency with cytologic observations of the human X and Y chromosomes, suggesting that there may be no truly homologous segments. (See Fig. 27.)

632. Hallman and Hjelt described 18 infants with *congenital nephrosis.* They were distributed in twelve sibships containing a total of 49 children. In the same sibships there were also 11 premature offspring who died in the newborn period. Whether there was a relationship to the congenital nephrosis is unknown but suspected. All affected infants died before the age of 19 months. Electron

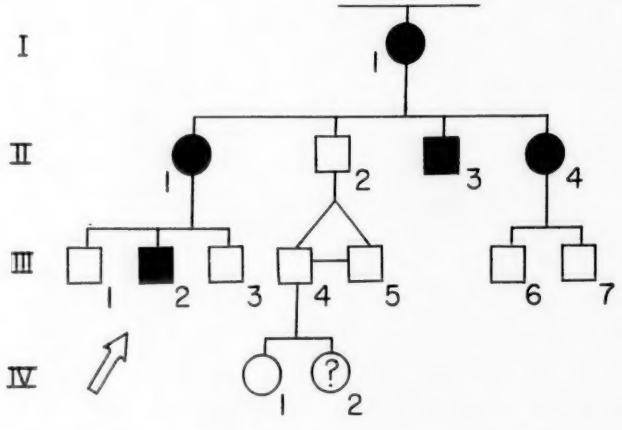


Fig. 27*A*.—Pedigree of a family with hereditary nephritis. I 1 died of chronic nephritis at age 65. II 1 died of chronic nephritis at age 52 (appearance shown in *B*); deaf. II 2 died of chronic nephritis at age 32. II 3 died of chronic nephritis at age 30. III 2 died of chronic nephritis at age 30; had moderately severe nerve deafness. Pathologic examination was performed in none of these cases.

microscopy in 3 cases revealed typical absence of foot processes and splitting of the basement membranes in the renal glomeruli—morphologic features of the nephrotic syndrome due to many different causes. Worthen, Vernier, and Good studied 12 cases of the nephrotic syndrome occurring within the first year of life. There was a "familial incidence" in 5 of the 12. The mothers of the familial cases all had toxemia during pregnancy.

633. The preponderance of phenotypic males among fetuses with *bilateral renal agenesis* (as well as the frequent association of genital anomaly) prompted Carpentier and Patter to study nuclear sex in 48 cases. In each case nuclear sex was appropriate to the external genitals. However, 4 of the cases had nonspecific female pseudohermaphroditism, bringing the total number in the literature to 23. Rosenfeld mentioned 2 male offspring who died a few hours after birth from renal agenesis. A female sibling was normal.

VOL. 12 1960

634. In an article concerned mainly with the surgical repair of *hypospadias*, Ross, Farmer, and Lindsay mentioned that out of 108 cases 14 per cent had a history of at least one other case in the family. Out of 230 cases, 20 per cent (or 42 patients) had associated anomalies such as undescended testes (in 26), inguinal hernia (in 10), and cardiovascular anomalies (in 6).

XXIV. MISCELLANEOUS

635. Jacobs, Shafer, and Higdon noted familial aggregation in *congenital branchiogenous anomalies.* Bhaskar and Bernier conclude that the majority (96 or 97 per cent) of "branchial cysts" are the result of trapping of epithelium

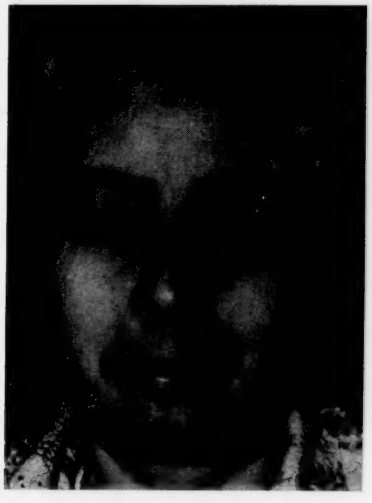


Fig. 27*B*.—H. A. L. (J.H.H. 399428) showed hyperpigmentation due probably to chronic uremia and had progressive deafness; note the hearing aid. II 1 of the pedigree.

in cervical lymph nodes and therefore more appropriately termed "benign cystic lymph nodes" or "benign lymphoepithelial cysts." The cysts are surrounded by lymphoid tissue, have no connection with the skin surface or pharynx, may occur also in the parotid, usually become evident in the third decade of life, and may show exacerbations in relation to upper respiratory and dental infections. Treatment is enucleation. A genetic basis is probably less definite than in the case of true branchial cleft cyst.

636. Kendig, Peacock, and Ryburn found *sarcoidosis* in 3 Negro siblings under 15 years of age (see ¶289).

637. Alkalay, Shenfield, and Levy found 4 members of one family (father and 3 sons) with *familial periodic disease* (familial Mediterranean fever). All

showed evidence of renal damage and one died at the age of 16 years of renal failure. Autopsy revealed generalized amyloidosis. (See ¶282.) Lawrence and Mellinkoff described 4 patients with Mediterranean fever manifested by short, self-limited episodes of fever, benign peritonitis, pleuritis, arthritis, and erysipeloid skin lesions. The patients were Armenian, Greek, or non-Ashkenazi (Mediterranean) Jewish. High urinary histidine excretion was found, but the authors concluded it was probably an anthropologic characteristic and not related to the disease. Priest and Nixon described cases.

638. Esguerra Gómez and collaborators described 4 sisters with *pulmonary alveolar microlithiasis.* These were the first cases reported from Colombia. The pathologic feature, illustrated by autopsy in the oldest of the 4 sisters, is the presence of innumerable minute concretions lying free within the alveoli throughout the lungs. Cough is a late manifestation. Cor pulmonale may supervene and is, in fact, the principal cause of symptoms and of death. In the literature the authors could find 43 familial cases of this disease. However, they suggest that the familial aggregation may be in part or wholly on the basis of an environmental factor: The 4 patients lived all their lives in the same house and same locality, had the same environment and diet, and were found to have the disease between ages 40 and 50 years. On the other hand, the other 3 siblings (one female, 2 males) left home at an early age and showed no sign of disease. The classic publication on the familial occurrence of pulmonary alveolar microlithiasis is that of Sosman and colleagues (Am. J. Roentgenol. 77:947, 1957). They reported 23 new cases of which 13 occurred in five families—a brother and 2 sisters, 4 sisters (2 brothers unaffected), 2 brothers, 2 sisters, a brother and sister. (Two sisters described by Sosman were probably 2 of the 4 sisters described by Esquerra Gómez and colleagues.) They speculated about "an inborn error of respiratory metabolism at the alveolar interface, possibly an enzyme fault."

639. Donohue and his colleague (see also Laski and colleagues) described 5 infants, in three families, dying of progressive pulmonary insufficiency and demonstrating, pathologically, changes like those described in the Hamman-Rich syndrome. They suggested the designation of "*familial fibrocystic pulmonary dysplasia.*" In the family with 3 affected siblings, 4 adults had chronic pulmonary disease. On reviewing 87 cases of the Hamman-Rich syndrome in the literature the authors found that 14 were familial. The data are consistent with autosomal dominant inheritance, but the lack of a definite instance of male-to-male transmission makes sex-linked dominant inheritance a possibility. This is probably the same disease as that reported by McKusick and Fisher (¶286).

640. Klaus and Brunsting wrote on *the Melkersson syndrome*, a rare disorder consisting of the triad of lingua plicata, recurrent facial paralysis, and recurrent—eventually permanent—facial edema. The role of genetic factors in its cause is uncertain. Lingua plicata appears to be congenital and not the result of repeated edema in the tongue. This peculiarity of the tongue was said by Cockayne to

VOL. 12 1960

be inherited as an irregular dominant trait. The authors quote Ekbom (1950) as suggesting that furrowed tongue is an indication of hereditary predisposition to facial paralysis (and facial edema).

641. Goldberg and Pittman reported a case of *cold sensitivity* (synonyms: cold allergy and cold urticaria). Although clinically there were similarities to the familial cases, there were no other cases in the family of their patient. Passive transfer of the phenomenon has been demonstrated in familial cold urticaria.

642. Towner described *Henoch-Schönlein purpura* in a brother (after diphtheria-pertussis immunization) and sister (after upper respiratory infection).

Van Arsdel and Motulsky did a questionnaire study of *asthma and allergic rhinitis* in 4,110 men and 1,708 women at the University of Washington. Allergy of one or both expressions was found in 16.7 per cent, 12 per cent had hay fever only, 2 per cent had asthma only, and 2.7 per cent had both.

L.
2
60

TABLE XII. PROPORTIONS OF ALLERGIC OFFSPRING BY ALLERGIC STATUS OF PARENTS

	STUDENTS		PROPORTION OF ALLERGIC
STATUS OF PARENTS	NONALLERGIC	ALLERGIC	OFFSPRING
Both parents allergic	21 (0.4%)	29 (3.0%)	58.0%
One parent allergic	521 (10.5%)	325 (33.4%)	38.4%
Neither parent allergic	4,305 (89.0%)	617 (63.5%)	12.5%

The authors concluded that the results "could not have occurred by chance alone due to a high population incidence of allergy coupled with under reporting in a non-allergic population." It would be difficult to be certain that improved knowledge of an allergic family history by allergic probands could not account in part for the findings. The authors concluded that a genetic factor is involved because of a number of findings which could not easily be accounted for on another basis: More parents of allergic students were allergic than would be expected if the incidence were the same as in the whole student group (19.7 per cent versus 16.7 per cent). The parents of nonallergic students were reported to be allergic in a proportion of 5.6 per cent. Parents of students with both hay fever and asthma had a 26.6 per cent frequency of allergy. The proportions of affected offspring according to whether both, one, or neither parent was affected (see Table XII) were consistent with the genetic hypothesis.

The authors provided an interesting tabulation of the probability of at least one family member being affected with asthma and/or hay fever by chance alone, assuming a 16.7 per cent incidence of these conditions. If N is the number of known family members, the probability in question is $1 - (0.833)^N$. With only 5 medically known family members, the probability becomes 60 per cent!

Although twinning was inquired into by the questionnaire, the data are not given—possibly because the authors suspected excessive error in classification of zygosity. The incidence of affected offspring according to whether the father or the mother was the one parent affected would be of interest as would also the sex ratio of affected individuals under these two contrasting circumstances. The authors did provide data on the frequency of a positive family history according to whether the student proband was male or female. The frequency of positive family history was higher for female probands. As has been revealed by other similar studies, women are better informed about the medical (and other) details of their relatives.

In another report Van Arsdel and Motulsky concluded that the ABO, Rh, and secretor frequencies in allergic persons are not different from those in the general population.

Klinker and Schnyder found no familial aggregation for contact eczema, urticaria, and drug allergy. Furthermore, in the families of probands with these disorders he found no increased frequency of allergy, hay fever, or atopic dermatitis. From this they concluded—assuming that a familial aggregation for allergy, hay fever, and atopic dermatitis is proved—that the two groups of conditions are fundamentally distinct.

643. Certain aspects of *comparative genetic pathology* are discussed in ¶'s 339, 340, 345, 359, 416, 470, 502, 504*e*, 504*m*, 533, 568, 598, 607, and 612. In addition, Jones discussed ataxia in foals; Schnelle and Innes, hip dysplasia in the dog; Swanton, hemophilic arthropathy in the dog; and Hadlow, the myopathies of livestock.

VOL. 12 196C

REFERENCES

Aagenaes, *ϕ.*: Hereditary Spastic Paraplegia, Acta psychiat. et neurol. scandinav. **34**:489, 1959.
Abrams, J., and Schwartz, I. R.: The Sickle Cell Diseases in Pregnancy, Am. J. Obst & Gynec. **77**:1324, 1959.
Adler, S.: Darwin's Illness, Nature, London, **184**:1102, 1959.
Aldersberg, D., Feldman, E. B., Kaplan, S., and Wang, C.-I.: Hyperlipemia and Pancreatitis, Hypercholesteremia and Coronary Artery Disease Complicating Pregnancy, Obstetrics **78**:851, 1959.
Adlersberg, D., and Schaefer, L. E.: The Interplay of Heredity and Environment in the Regulation of Circulating Lipids and in Atherogenesis, Am. J. Med. **26**:1, 1959.
Ahuja, Y. R.: L'hérédité de l'arcus corneae, J. génét. humaine **8**:95, 1959.
Aird, I.: Conjoined Twins—Further Observations, Brit. M. J. **1**:1313, 1959.
Akesson, H. O.: Taste Sensitivity to Phenyl-thio-urea in Tuberculosis and Diabetes Mellitus, Ann. Human Genet. **23**:262, 1959.
Aksov, M.: Thalassaemia Minor With Large Amount of Fetal Haemoglobin, Report of Four Cases, Acta haemat. **22**:188, 1959.
Albrink, M. J., and Man, E. B.: Serum Triglycerides in Coronary Artery Disease, A.M.A. Arch. Int. Med. **103**:4, 1959.
Album, M. M.: Progeria—Case Report, J. Den. Children, Second Quarter, 1959, p. 106.
Alkalay, I., Shenfield, M., and Levy, E.: Familial Periodic Disease With Renal Damage, J.A.M.A. **170**:653, 1959.
Allan, T. M.: ABO Blood Groups and Sex Ratio at Birth, Brit. M. J. **1**:553, 1959.
Allen, H. L., Metcalf, D. W., and Giering, C.: Anesthetic Management for the Separation of Conjoined Twins, Anesth. & Analg. **38**:109, 1959.
Allison, A. C.: Genetic Control of Human Haptoglobin Synthesis, Nature, London **183**:1312, 1959.
Allison, A. C.: Haptoglobins, Blut **5**:201, 1959.
Allison, A. C.: Identification of Human Serum Proteins Binding Iron, Copper, and Thyroid Hormones by Starch Gel Electrophoresis, Experientia **15**:281, 1959.

Allison, A. C.: Metabolic Polymorphisms in Mammals and Their Bearing on Problems of Biochemical Genetics, Am. Naturalist **93**:5, 1959.
Allison, A. C.: Recent Developments in the Study of Inherited Anemias, Eugenics Quart. **6**:155, 1959.
Allison, A. C., Blumberg, B. S., and Gartler, S. M.: Urinary Excretion of Beta-Aminoisobutyric Acid in Eskimo and Indian Populations of Alaska, Nature, London **183**:118, 1959.
Almond, T. H.: Five Duodenal Ulcers in a Sibship, Brit. M. J. **1**:1332, 1959.
Alper, R. G., Cavanagh, D., and Jonsson, U.: Sickle cell–Hemoglobin C Disease; Report of a Case Associated With Sudden Coma in the Puerperium, Obst. & Gynec. **13**:319, 1959.
Alström, C. H., Hallgren, B., Nilsson, L. B., and Asander, H.: Retinal Degeneration Combined With Obesity, Diabetes Mellitus and Neurogenous Deafness. A Specific Syndrome (Not Hitherto Described) Distinct From the Laurence-Moon-Bardet-Biedl Syndrome. A Clinical, Endocrinological and Genetic Examination Based on a Large Pedigree, Acta psychiat. et neurol. scandinav. **34**:suppl. 129:1-35, 1959.
Alvarez, W. C.: The Nature of Charles Darwin's Lifelong Ill-Health, New England J. Med. **261**: 1109, 1959.
Anderson, V. E.: Review of Monograph by Murphy and Abbey, Am. J. Human Genet. **11**:388, 1959.
Andrew, L. E.: The Mutagenic Activity of Caffein in Drosophila, Am. Naturalist **93**:135, 1959.
Annotation: Conjoined Twins, Brit. M. J. **1**:1337, 1959.
Archibald, R. M., Finby, N., and DeVito, F.: Endocrine Significance of Short Metacarpals, J. Clin. Endocrinol. **19**:1312, 1959.
Arends, T., Layrisse, M., and Rincon, A. R.: Sickle Cell–Haemoglobin D Disease in a Portuguese Child, Acta haemat. **22**:118, 1959.
Arias, I. M.: Gilbert's Disease, Bull. New York Acad. Med. **35**:450, 1959.
Arnvig, J.: The Syndrome of Waardenburg, Acta genet. **9**:41, 1959.
Aronson, S. A., Aronson, B. E., and Volk, B. W.: A Genetic Profile of Infantile Amaurotic Family Idiocy, A.M.A. J. Dis. Child. **98**:50, 1959.
Ashley, D.: The Technic of Nuclear Sexing, Am. J. Clin. Path. **31**:230, 1959.
Ashley, D. J. B.: Are Ovarian Pregnancies Parthenogenetic? Am. J. Human Genet. **11**:305, 1959.
Ashton, G. C.: Beta-Globulin Alleles in Some Zebu Cattle, Nature, London **184**:1135, 1959.
Ashton, G. C.: Beta-Globulin Polymorphism and Early Foetal Mortality in Cattle, Nature, London **183**:404, 1959.

Baer, P., and Leiberman, J. E.: Observation on Some Genetic Characteristics of the Periodontium in Three Strains of Inbred Mice, Oral Surg. **12**:820, 1959.
Baikie, A. G., Brown, W. M. Court, Jacobs, P. A., and Milne, J. S.: Chromosome Studies in Human Leukaemia, Lancet **2**:425, 1959.
Bannerman, R. M., Grinstein, M., and Moore, C. V.: Haemoglobin Synthesis in Thalassaemia: In-Vitro Studies, Brit. J. Haemat. **5**:102, 1959.
Barbeau, A., Reilly, R. W., and Kirsner, J. B.: An Early Defect in Wilson's Syndrome (Abstract), J. Lab. & Clin. Med. **54**:786, 1959.
Barber, M., and Dunsford, I.: Excess Blood-Group Substance A in Serum of Patient Dying With Carcinoma of Stomach, Brit. M. J. **1**:607, 1959.
Barnes, H. D.: The Excretion of Porphyrins and Porphyrin Precursors by Bantu Cases of Porphyria, South African M. J. **33**:274, 1959.
Barr, M. L.: Sex Chromatin, Science **130**:1302, 1959.
Barr, M. L.: Sex Chromatin and Phenotype in Man, Science **130**:679, 1959.
Bartholomew, L. G.: Newer Concepts in Pancreatic Disease, Gastroenterology **36**:122, 1959.
Beard, A.: The Association of Hepatolenticular Degeneration With Schizophrenia, Acta psychiat. et neurol. scandinav. **34**:411, 1959.
Bearn, A. G.: Genetic Aspects of Wilson's Disease, Proc. Roy. Soc. Med. **52**:61, 1959.
Bearn, A. G., and Franklin, E. C.: Comparative Studies on the Physical Characteristics of the Heritable Haptoglobin Groups of Human Serum, J. Exper. Med. **109**:55, 1959.
Bearn, J. G.: The Male Anencephalic Foetus, Lancet **2**:464, 1959.
Bearn, J. G.: Nuclear Chromatin of Anencephalic Foetuses, Lancet **2**:24, 1959.
Beaven, G. H., and Gratzer, W. B.: A Critical Review of Human Haemoglobin Variants. I. Methods for Separation and Characterization, J. Clin. Path. **12**:1, 1959; II. Individual Haemoglobins, J. Clin. Path. **12**:101, 1959.
Beaven, G. H., and Gratzer, W. B.: Foetal Haemoglobin in the Monkey, Nature, London **184**:1730, 1959.
Beckman, L., Broman, B., Jonsson, B., and Mellbin, T.: Further Data on the Blood Groups of the Swedish Lapps, Acta genet. **9**:1, 1959.
Beierwaltes, W. H., Dodson, V. N., and Wheeler, A. H.: Thyroid Autoantibodies in the Families of Cretins, J. Clin. Endocrinol. **19**:179, 1959.
Beierwaltes, W. H., and Robbins, J.: Familial Increase in the Thyroxine-Binding Sites in Serum Alpha Globulin, J. Clin. Invest. **38**:1683, 1959.
Bell, R. F., and Williams, H. L.: Threshold Values for Taste in Monozygotic Twin Calves, Nature, London **183**:345, 1959.

Bender, S.: Twins and Heredity, Practitioner **183**:183, 1959.
Bennet, J. H., Rhodes, F. A., and Robson, H. N.: A Possible Genetic Basis for Kuru, Am. J. Human Genet. **11**:169, 1959.
Bennhold, H., and Kallee, E.: Comparative Studies on the Half-Life of I^{131}-Labeled Albumins and Nonradioactive Human Serum Albumin in a Case of Analbuminemia, J. Clin. Invest. **38**:863, 1959.
Berg, J. M., Brandon, G., and Kirkman, B. H.: Atropine in Mongolism, Lancet **2**:441, 1959.
Bernstein, J., and Shelden, W. E.: A Note on the Development of Gaucher Cells in a Newborn Infant, J. Pediat. **55**:577, 1959.
Berry, H. K.: Cystinuria in Mentally Retarded Siblings With Atypical Osteogenesis Imperfecta, A.M.A. J. Dis. Child. **97**:196, 1959.
Beutler, E.: The Hemolytic Effect of Primaquine and Related Compounds: A Review, Blood **14**:103, 1959.
Beutler, E., Yeh, M. K. Y., and Necheles, T.: Incidence of Erythrocyte Defect Associated With Drug-Sensitivity Among Oriental Subjects, Nature, London **183**:1266, 1959.
Bigler, J. A., Mais, R. F., Dowben, R. M., and Hsia, D. Y.-Y.: An Inborn Error of Lipid Metabolism, Pediatrics **23**:644, 1959.
Bigwood, E. J., Crokaert, R., Schram, E., Soupart, P., and Vis, H.: Amino Aciduria, *in* Sobotka, H., and Stewart, C. P., editors: Advances in Clinical Chemistry, vol. 2, New York, 1959, Academic Press, Inc.
Bihl, J. H.: The Effect of Pregnancy on Hepatolenticular Degeneration (Wilson's Disease): Report of a Case, Am. J. Obst. & Gynec. **78**:1182, 1959.
Billing, B. H.: Bile Pigments in Jaundice, *in* Sobotka, H., and Stewart, C. P., editors: Advances in Clinical Chemistry, vol. 2, New York, 1959, Academic Press, Inc.
Billingham, R. E.: Reactions of Grafts Against Their Hosts, Science **130**:947, 1959.
Bird, A. V., and Mendelow, H.: Lindau's Disease in a South African Family, Brit. J. Surg. **47**:173, 1959.
Bird, R. M., and Jaques, W. E.: Vascular Lesion of Hereditary Hemorrhagic Telangiectasia, New England J. Med. **260**:597, 1959.
Blanc, W. A., and Johnson, L.: Studies on Kernicterus. Relationship With Sulfonamide Intoxication, Report on Kernicterus in Rats With Glucuronyl Transferase Deficiency and Review of Pathogenesis, J. Neuropath. & Exper. Neurol. **18**:165, 1959.
Blassingille, B.: A Rare Form of Ectodermal Dysplasia, Neurology **9**:384, 1959.
Blattner, R. J.: Infantile Agranulocytosis of Congenital Origin, J. Pediat. **54**:6, 1959.
Bleifer, S. B., and Alphas, S. J.: Acute Intermittent Porphyria, New England J. Med. **260**:978, 1959.
Bloom, D.: Genodermatoses, M. Clin. North America **43**:1, 1959.
Blumberg, B. S., and Gartler, S. M.: High Prevalence of High-Level Beta-Amino-Isobutyric Acid Excretors in Micronesians, Nature, London, **184**:1990, 1959.
Blumel, J., and Kniker, W. T.: Laurence-Moon-Bardet-Biedl Syndrome, Texas Rep. Biol. & Med. **17**:391, 1959.
Blyth, H., and Pugh, R. J.: Muscular Dystrophy in Childhood; the Genetic Aspect; a Field Study in the Leeds Region of Clinical Types and Their Inheritance, Ann. Human Genet. **23**:127, 1959.
Boackle, L. A.: A Familial Study in Porphyrias and Porphyrinurias, Am. J. M. Technol. **25**:33, 1959.
Böök, J. A., Fraccaro, M., and Lindsten, J.: Cytogenetical Observations in Mongolism, Acta paediat. **48**:453, 1959.
Boileau, P. A., and Dionne, L.: Le syndrome de Ehlers-Danlos et grossesse, Union méd. Canada **88**:285, 1959.
Bolton, F. G., and Clarke, J. E.: A Method of Assaying Christmas Factor; Its Application to the Study of Christmas Disease (Factor-IX Deficiency), Brit. J. Haemat. **5**:396, 1959.
Borchgrevink, C. F., and Coauthors: A Study of a Case of Congenital Hypoprothrombinaemia, Brit. J. Haemat. **5**:294, 1959.
Boström, H.: Cystinuria in Sweden. III. The Prognosis of Homozygous Cystinuria, Acta chir. scandinav. **116**:287, 1959.
Boström, H., and Tottie, K.: Cystinuria in Sweden. II. The Incidence of Homozygous Cystinuria in Swedish Schoolchildren, Acta paediat. **48**:345, 1959.
Bothwell, T. H., Cohen, I., Abrahams, O. L., and Perold, S. M.: A Familial Study in Idiopathic Hemochromatosis, Am. J. Med. **27**:730, 1959.
Bourne, G. H., and Golarz, M. N.: Human Muscular Dystrophy as an Aberration of the Connective Tissue, Nature, London **183**:1741, 1959.
Bowers, D.: Marfan's Syndrome and Weill-Marchesani Syndrome in the S. Family, Ann. Int. Med. **51**:1049, 1959.
Boyd, M. W. J., and Grant, A. P.: Werner's Syndrome (Progeria of the Adult); Further Pathological and Biochemical Observations, Brit. M. J. **2**:920, 1959.
Boyo, A. E., and Hendrickse, R. G.: New Fast Abnormal Haemoglobin in Newborn Nigerians, Nature, London **184**:997, 1959.

VOL. 12 1960

Bozian, R. C., and Touster, O.: Essential Pentosuria: Renal or Enzymatic Disorder, Nature, London **184**:463, 1959.
Brandon, M. G., Kirman, B. H., and Williams, C. E.: Microcephaly in One of Monozygous Twins, Arch. Dis. Childhood **34**:56, 1959.
Bremner, J. M., Alexander, W. R. M., and Duthie, J. J. R.: Familial Incidence of Rheumatoid Arthritis, Ann. Rheumat. Dis. **18**:279, 1959.
Brescia, M. A., Santora, E., and Sarnataro, V. F.: Congenital Leukemia, J. Pediat. **55**:35, 1959.
Bretthauer, R. K., Hansen, R. G., Donnell, G., and Bergson, W. R.: A Procedure for Detecting Carriers of Galactosemia, Proc. Nat. Acad. Sc. **45**:328, 1959.
Brinkhous, K. M., and De Nicola, P., editors: Hemophilia and Other Hemorrhagic States, Chapel Hill, 1959, University of North Carolina Press.
Brodal, A., and Hauglie-Hanssen, E.: Congenital Hydrocephalus With Defective Development of the Cerebellar Vermis (Dandy Walker Syndrome). Clinical and Anatomical Findings in Two Cases With Particular Reference to the So-called Atresia of the Foramina of Magendie and Luschka, J. Neurol. Neurosurg. & Psychiat. **22**:99, 1959.
Brogan, T. D.: The Carbohydrate Complexes of Bronchial Secretion, Biochem. J. **71**:125, 1959.
Brown, J. R.: Degenerative Cerebellar Ataxias, Neurology **9**:799, 1959.
Brown, P. C., Glynn, L. E., and Holborow, E. J.: Lewis Substance in Salvia. A Qualitative Difference Between Secretors and Nonsecretors, Vox Sang. **4**:1, 1959.
Brown, W. M. Court, and Doll, R.: Adult Leukemia. Trends in Mortality in Relation to Etiology, Brit. M. J. **1**:1063, 1959.
Brubaker, C., and Hammond, D.: Familial Sex-Linked Thrombocytopenia: Response to Splenectomy, Clin. Res. **7**:57, 1959.
Bryan, R. S., and Dimichele, J. D.: Osteogenesis Imperfecta. Report of 6 Familial Cases, U. S. Armed Forces M. J. **10**:312, 1959.
Bryant, J. M., and Bozian, R. C.: A New Specific Genetic Tool (Abstract), J. Lab. & Clin. Med. **54**:795, 1959; also *in* Kossmann, C. E., editor: Advances in Electrocardiography, New York, 1958, Grune & Stratton.
Buckwalter, J. A., and Coauthors: Psychoses, Intracranial Neoplasms, and Genetics, A.M.A. Arch. Neurol. & Psychiat. **81**:480, 1959.
Bulmer, M. G.: The Effect of Parental Age, Parity and Duration of Marriage on the Twinning Rate, Ann. Human Genet. **23**:454, 1959.
Bulmer, M. G.: Twinning Rate in Europe During the War, Brit. M. J.: **1**:29, 1959.
Bunge, R. G., and Bradbury, J. T.: Two Unilaterally Cryptorchid Boys With Spermatogenic Precocity in the Descended Testis, Hypertelorism and Polydactyly, J. Clin. Endocrinol. **19**:1103, 1959.
Bunner, R.: Lateral Intrathoracic Meningocele, Acta radiol. **51**:1, 1959.
Burghele, T., Joachim, B., and Goldstein, J.: Recklinghausen's Disease With Urinary Manifestations: Neurofibroma of the Bladder, Am. J. Surg. **97**:108, 1959.
Burnet, M.: Virus Genetics, Brit. M. Bull. **15**:177, 1959.

Cabannes, R., and Portier, A.: *in* Jonxis, J. H. P., and Delafresnaye, J. S., editors: Abnormal Haemoglobins, Oxford, 1959, Blackwell Scientific Publications.
Cabot Case 45271: Carcinoma of the Stomach in 17-Year-Old Male With Mongolism, New England J. Med. **261**:39, 1959.
Caen, J., Yanotti, S., Varangot, J., and Bernard, J.: Étude d'un cas d'hypoproconvertinemie vraie congénitale, Sang **30**:535, 1959.
Campbell, M.: The Genetics of Congenital Heart Disease and Situs Inversus in Sibs, Brit. Heart J. **21**:65, 1959.
Cameron, J. M.: Familial Incidence of Mixed Salivary Tumours, Scot. M. J. **4**:455, 1959.
Capper, A.: Cystinosis, J. Albert Einstein M. Center **7**:41, 1959.
Carlborg, V., Ejrup, B., Grönbald, E., and Lund, F.: Vascular Studies in Pseudoxanthoma Elasticum, With a Series of Color Photographs of the Eyeground Lesions, Acta med. scandinav., suppl. 350, 1959.
Carlson, E. A.: Comparative Genetics of Complex Loci, Quart. Rev. Biol. **34**:33, 1959.
Carnevali, J. F., and Kunath, C. A.: Congenital Absence of the Gallbladder, A.M.A. Arch. Surg. **78**:440, 1959.
Carpentier, P. J., and Potter, E. L.: Nuclear Sex and Genital Malformation in 48 Cases of Renal Agenesis, With Especial Reference to Nonspecific Female Pseudohermaphroditism, Am. J. Obst. & Gynec. **78**:235, 1959.
Carr, E. A., Beierwaltes, W. H., and Clure, H.: A Latent Thyroid Defect in "Normal" Mothers of Cretins, Clin. Res. **7**:388, 1959.
Carson, P. E., Schrier, S. L., and Kellermeyer, R. W.: Mechanism of Inactivation of Glucose-6-Phosphate Dehydrogenase in Human Erythrocytes, Nature, London **184**:1292, 1959.
Carter, C. O., Sheldon, W., and Walker, C.: The Inheritance of Coeliac Disease, Ann. Human Genet **23**:266, 1959.
Carter, C. O.: Heredity and Congenital Malformations, Practitioner **183**:144, 1959.
Caughey, J. E., and Pachomov, N.: The Diaphragm in Dystrophia Myotonica, J. Neurol. Neurosurg. & Psychiat. **22**:311, 1959.

Cervanansky, J., Sitaj, S., and Urbanek, T.: Alkaptonuria and Ochronosis, J. Bone & Joint Surg. **41A**:1169, 1959.
Chadoutaud, L.: Favism, Presse méd. **67**:132, 1959.
Champion, R., and Cregan, J. C. F.: Congenital Popliteal Webbing in Siblings, J. Bone & Joint Surg. **41B**:355, 1959.
Chang, C.-P.: Studies on the Chromosomes of Human Oogonia, Jap. J. Human Genet. **4**:196, 1959.
Chao, D. H.-C.: Congenital Neurocutaneous Syndromes in Childhood. II. Tuberous Sclerosis, J. Pediat. **55**:447, 1959.
Chao, D. H.-C.: Congenital Neurocutaneous Syndromes in Childhood. III. Sturge-Weber Disease, J. Pediat. **55**:635, 1959.
Chapman, R. C., Kemp, V. E., and Taliaferro, I.: Pheochromocytoma Associated With Multiple Neurofibromatosis and Intracranial Hemangioma, Am. J. Med. **26**:883, 1959.
Chaudhry, A. P.: Hereditary Enamel Dysplasia, J. Pediat. **54**:776, 1959.
Chernoff, A. I.: The Distribution of the Thalassemia Gene; a Historical Review, Blood **14**:899, 1959.
Chevallier, P., and Coauthors: Déficience congénitale et familiale en facteur Stuart, Sang **30**:525, 1959.
Childs, B.: Hereditary Aspects of Disease, Bull. New York Acad. Med. **35**:77, 1959.
Childs, B., Sidbury, J. B., and Migeon, C. J.: Glucuronic Acid Conjugation by Patients With Familial Nonhemolytic Jaundice and Their Relatives, Pediatrics **23**:903, 1959.
Choremis, C., Kiossoglou, K., Maounis, F., and Basti, B.: Amino-acid Tolerance Curves and Amino-aciduria in Cooley's and Sickle-Cell Anaemias, J. Clin. Path. **12**:245, 1959.
Choremis, K., Papadatos, C., and Caterellos, C.: Familial Multilocular Cystic Disease of the Jaws, Helvet. paediat. acta **14**:396, 1959.
Chou Yi-Che: Ocular Signs in Gargoylism, Report of a Case, Chinese M. J. **78**:130, 1959.
Christensen, H. N.: Active Transport, With Special Reference to the Amino Acids, Perspectives Biol. & Med. **2**:228, 1959.
Chu, E. H., and Giles, N. H.: Human Chromosome Complements in Normal Somatic Cells in Culture, Am. J. Human Genet. **11**:63, 1959.
Chung, C. S., and Morton, N. E.: Discrimination of Genetic Entities in Muscular Dystrophy, Am. J. Human Genet. **11**:339, 1959.
Chung, C. S., Robison, O. W., and Morton, N. E.: A Note on Deaf Mutism, Ann. Human Genet. **23**:357, 1959.
Clarke, C. A.: Correlation of ABO Blood Groups and Peptic Ulcer, Cancer, and Other Diseases, J. M. Educ. **34**:400, 1959.
Clarke, C. A.: Distribution of ABO Blood Groups and the Secretor Status in Duodenal Ulcer Families, Gastroenterologia **92**:99, 1959.
Clarke, C. A., Evans, D. A. P., McConnell, R. B., and Sheppard, P. M.: Secretion of Blood Group Antigens and Peptic Ulcer, Brit. M. J. **1**:603, 1959.
Cleghorn, T. E.: A "New" Human Blood Group Antigen Sw_a, Nature, London **184**:1324, 1959.
Clement, R.: La fragilité osseuse héréditaire, Presse méd. **67**:1421, 1959.
Cochrane, W. A., and Moya, F.: The Relationship of Amino Acids to Idiopathic Hypoglycemia, A.M.A. J. Dis. Child. **98**:26, 1959.
Coffey, V. P., and Jessop, W. J. E.: Maternal Influenza and Congenital Deformities: A Prospective Study, Lancet **2**:935, 1959.
Coffman, J. D., and Sommers, S. C.: Familial Pseudoxanthoma Elasticum and Valvular Heart Disease, Circulation **19**:242, 1959.
Cohen, B. H., and Glass, B.: The Relation of the ABO and Rh Blood Groups to Differential Reproduction, J. M. Educ. **34**:414, 1959.
Cole, J. W., and Holden, W. D.: Postcolectomy Regression of Adenomatous Polyps of the Rectum, A.M.A. Arch. Surg. **79**:385, 1959.
Cole, R. B. W.: The Problem of Unilateral Amblyopia, Brit. M. J. **1**:202, 1959.
Coleman, P. N., Edmunds, A. W. B., and Tregillus, J.: Primary Pulmonary Hypertension in Three Sibs, Brit. Heart J. **21**:81, 1959.
Collins, D. C.: The Frequent Association of Other Body Tumors With Familial Polyposis, Am. J. Gastroenterol. **31**:376, 1959.
Collipp, P. J., and Donnell, G. N.: Galactosemia Presenting With Gangrene, J. Pediat. **54**:363, 1959.
Connell, G. E., and Smithies, O.: Human Haptoglobins: Estimation and Purification, Biochem. J. **72**:115, 1959.
Cooper, I. S.: Dystonia Musculorum Deformans Alleviated by Chemopallidectomy and Chemopallidothalamectomy, A.M.A. Arch. Neurol. & Psychiat. **81**:5, 1959.
Cornelius, C. E., Law, G. R. J., Julian, L. M. and Asmundson, V. S.: Plasma Aldolase and Glutamic-Oxaloacetic Transaminase Activities in Inherited Muscular Dystrophy of Domestc Chicken, Proc. Soc. Exper. Biol. & Med. **101**:41, 1959.
Cowie, V.: Heredity and Mental Disease, Practitioner **183**:152, 1959.
Crew, F. A. E.: Heredity and Sex-Determination, Practitioner **183**:178, 1959.
Cruz-Coke, R.: The Hereditary Factor in Hypertension, Acta genet. **9**:207, 1959.

VOL. 12 1960

Cuadrillero, C. B.: Stains for Sex Chromatin: Silver Impregnation in Tissues and Blood Films, Stain Technol. **34**:290, 1959.
Curnow, D. H., Morgan, E. H., and Sarfaty, G. A.: Acute Intermittent Porphyria: A Family Study, Australasian Ann. Med. **8**:267, 1959.
Curth, H. O., and Aschner, B. M.: Genetic Studies on Acanthosis Nigricans, A.M.A. Arch. Dermat. **79**:55, 1959.
Curtis, E. M.: Pregnancy in Sickle Cell Anemia, Sickle Cell–Hemoglobin C Disease, and Variants Thereof, Am. J. Obst. & Gynec. **77**:1312, 1959.

Daly, D., Siekert, R. G., and Burke, E. C.: A Variety of Familial Light Sensitive Epilepsy, Electroencephalography **11**:141, 1959.
Daly, D. D., and Yoss, R. E.: A Family With Narcolepsy, Proc. Staff Meet. Mayo Clin. **34**:313, 1959.
Dancaster, C. P., and Jackson, W. P. U.: Familial Vitamin D–Resistant Rickets, Arch. Dis. Childhood **34**:383, 1959.
Dancis, J.: Phenylketonuria and Maple Sugar Urine Disease, Bull. New York Acad. Med. **25**:427, 1959.
Dancis, J., Levitz, M., Miller, S., and Westall, R. G.: "Maple Syrup Urine Disease," Brit. M. J. **1**:91, 1959.
Darling, R. C., and Welch, C. E.: Tumors of the Small Intestine, New England J. Med. **260**:397, 1959.
Davidson, C. H.: Hereditary Haemorrhagic Telangiectasia: A Report on a Family of Seven Generations, Scot. M. J. **4**:260, 1959.
Dean, G., and Barnes, H. D.: Porphyria in Sweden and South Africa, South African M. J. **33**:246, 1959.
de Castro, N. M., and da Silva Sasso, W.: Sex Chromatin ("Chromoleme") in the Purkinje Nerve Cells of Some Mammals, Nature, London **184**:293, 1959.
DeGroot, L. J., and Stanbury, J. B.: The Syndrome of Congenital Goiter with Butanol-Insoluble Serum Iodine, Am. J. Med. **27**:586, 1959.
Dencker, S. J., Hauge, M., and Kaij, L.: An Investigation of the PTC Taste Character in Monochorionic Twin Pairs, Acta genet. **9**:236, 1959.
DePree, H. E., and Hickman, M. J.: Familial Congenital Methemoglobinemia: Report of a Case and Family Study, Ann. Int. Med. **51**:1078, 1959.
Deutsch, E., editor: Symposium on Blood Clotting Factors (IVth International Congress of Biochemistry, Vienna, 1958), New York, 1959, Pergamon Press.
DeVaal, O. M., and Seynhaeve, V.: Reticular Dysgenesis, Lancet **2**:1123, 1959.
Dherte, P., Lehmann, H., and Vandepitte, J.: Haemoglobin P in the Family in the Belgian Congo, Nature, London **184**:1133, 1959.
Dherte, P., Vandepitte, J., Ager, J. A. M., and Lehmann, H.: Stanleyville I and II. Two New Variants of Adult Haemoglobin, Brit. M. J. **2**:282, 1959.
Dhir, B. K., and Agarwai, R. C.: Marfan's Syndrome, J. Indian M. A. **33**:476, 1959.
Diamond, M.: Five Cases of Sickle-Cell Haemoglobin-C Disease, Lancet **2**:322, 1959.
Dickinson, C. J., and Smellie, J. M.: Xanthinuria, Brit. M. J. **2**:1217, 1959.
Didisheim, P.: An Artificial Reagent for the Diagnosis of Classical Hemophilia, Science **129**:389, 1959.
di Sant'Agnese, P. A.: Diseases of Glycogen Storage With Special Reference to the Cardiac Type of Generalized Glycogenesis, Ann. New York Acad. Sc. **72**:439, 1959.
Dische, F. E., and Benfield, V.: Congenital Factor VII Deficiency; Haematological and Genetic Aspects, Acta haemat. **21**:257, 1959.
Dodge, H. W., Jr., Wood, M. W., and Kennedy, R. L.: Craniofacial Dysostosis: Crouzon's Disease, Pediatrics **23**:98, 1959.
Donnell, G. N., Bergren, W. R., and Roldan, M.: Genetic Studies in Galactosemia, Pediatrics **24**:418, 1959.
Donohue, W. L., Laski, B., Uchida, I., and Mann, J. D.: Familial Fibrocystic Pulmonary Dysplasia and Its Relation to the Hamman-Rich Syndrome, Pediatrics **24**:786, 1959.
Dorr, A. D., and Moloney, W. C.: Acquired Pseudo-Pelger Anomaly of Granulocytic Leukocytes, New England J. Med. **261**:742, 1959.
Douglas, W. F., Schonholtz, G. J., and Geppert, L. J.: Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome), A.M.A. J. Dis. Child. **97**:473, 1959.
Downing, J. G.: Dermatology, New England J. Med. **260**:1223, 1959.
Dray, S., and Young, G. O.: Two Antigenically Different Gamma-Globulins in Domestic Rabbits Revealed by Isoprecipitins, Science **129**:1023, 1959.
Druez, G.: Un nouveau cas d'acanthocytose. Dysmorphie érythrocytaire congénitale avec rétinite, trouble nerveux et stigmates dégénératifs, Rev. hémat. **14**:3, 1959.
Dubiski, S., Dudziak, Z., and Skaba, S.: Serum Groups in Rabbits, Immunology **2**:84, 1959.
Dubiski, S., Skaba, D., Dubiska, A., and Kelus, A.: Iso-Antigens of Rabbit Gamma-Globulin, Nature, London **184**:1811, 1959.
Dunnill, M. S.: Metaplastic Changes in the Visceral Pleura in a Case of Fibrocystic Disease of the Pancreas, J. Path. & Bact. **77**:299, 1959.

Dunning, E. J.: Struma Lymphomatosa: 3 Cases in One Family, J. Clin. Endocrinol. **19**:1121, 1959.

Earle, D. B., Hutt, M. P., Schmid, K., and Gitlin, D.: Observations on Double Albumin, a Genetically Transmitted Serum Protein Anomaly, J. Clin. Invest. **38**:1412, 1959.
Editorial: Glycogen Metabolism, J.A.M.A. **171**:1966, 1959.
Edström, R., Gröntoft, O., and Sandring, H.: Refsum's Disease; Three Siblings, One Autopsy, Acta psychiat. et neurol. scandinav. **34**:40, 1959.
Egan, T. J., and Klein, R.: Hyperkalemic Familial Periodic Paralysis, Pediatrics **24**:761, 1959.
Eichwald, E. J., Lustgraaf, E. C., and Strainer, M.: Genetic Factors in Parabiosis, J. Nat. Cancer Inst. **23**:1193, 1959.
Eisner, V., Pauli, L. L., and Livingston, S.: Hereditary Aspects of Epilepsy, Bull. Johns Hopkins Hosp. **105**:245, 1959.
Ek, J. I.: Thyroid Function in Mothers of Mongoloid Infants, Acta paediat. **48**:33, 1959.
Elliott, G. A., Sandler, A., and Rabinowitz, D.: Gonadal Dysgenesis in 3 Sisters, J. Clin. Endocrinol. **19**:945, 1959.
Elsbach, L.: Bilateral Hereditary Micro-epiphyseal Dysplasia of the Hips, J. Bone & Joint Surg. **41A**:514, 1959.
Engel, W. K., Kurland, L. T., and Klatzo, I.: An Inherited Disease Similar to Amyotrophic Lateral Sclerosis With a Pattern of Posterior Column Involvement. An Intermediate Form? Brain **82**:203, 1959.
Enger, E.: Wilson's Disease. Report of Case With Normal Caeruloplasmin Level, Acta med. scandinav. **163**:121, 1959.
Engfeldt, B., Hulth, A., and Westerborn, O.: Effect of Papain on Bone, A.M.A. Arch. Path. **68**:600, 1959.
Epstein, F. H., Block, W. D., Hand, E. A., and Francis, T., Jr.: Familial Hypercholesterolemia, Xanthomatosis and Coronary Heart Disease, Am. J. Med. **26**:39, 1959.
Evans, J.: Treatment of Heart Failure in Haemochromatosis, Brit. M. J. **1**:1075, 1959.
Everberg, G.: Marfan's Syndrome Associated With Hearing Defect; Report of a Case in One of a Pair of Twins, Acta paediat. **48**:70, 1959.

Faivre, G., Gilgenkrantz, J.-M., and Panther, J.-J.: La cardiomégalie familiale, Presse méd. **67**:673, 1959.
Falek, A.: Handedness: A Family Study, Am. J. Human Genet. **11**:52, 1959.
Falkinburg, L. W.: Intestinal Polyposis With Oral Pigmentation, J. Pediat. **54**:2, 1959.
Farrar, T., and Chappell, F. W.: Severe Gastrointestinal Hemorrhage Resulting From Recklinghausen's Disease, A.M.A. Arch. Surg. **79**:106, 1959.
Feigin, I.: Demyelinating Diseases With Special Emphasis on the Metachromatic Type (Postnatal and Early Infantile), J. Neuropath. & Exper. Neurol. **18**:156, 1959.
Ferguson, M. J., and Clemente, A. R.: Rupture and Dissection of Aorta in Marfan's Syndrome, Am. J. Cardiol. **4**:543, 1959.
Ferguson-Smith, M. A.: The Prepubertal Testicular Lesion in Chromatin-Positive Klinefelter's Syndrome (Primary Micro-Orchidism) as Seen in Mentally Handicapped Children, Lancet **1**:219, 1959.
Fessas, P., Mastrokalos, N., and Fostiropoulos, G.: New Variant of Human Foetal Haemoglobin, Nature, London **183**:30, 1959.
Fisch, L.: Deafness as Part of an Hereditary Syndrome, J. Laryng. & Otol. **73**:355, 1959.
Fischer, R., and Griffin, F.: On Factors Involved in the Mechanism of "Taste-Blindness," Experientia **15**:447, 1959.
Fitzpatrick, T. B., and Szabo, G.: The Melanocyte: Cytology and Cytochemistry, J. Invest. Dermat. **32**:197, 1959.
Ford, C. E., and Coauthors: The Chromosomes in a Patient Showing Both Mongolism and the Klinefelter Syndrome, Lancet **1**:709, 1959.
Ford, C. E., and Coauthors: A Sex-Chromosome Anomaly in a Case of Gonadal Dysgenesis (Turner's Syndrome), Lancet **1**:711, 1959.
Ford, C. E., and Mole, R. H.: Chromosome Studies in Leukaemia, Lancet **2**:732, 1959.
Ford, C. E., Polani, P. E., Briggs, J. H., and Bishop, P. M. F.: A Presumptive Human XXY/XX Mosaic, Nature, London **183**:1030, 1959.
Forsythe, W. I., McKeown, E. F., and Neill, D. W.: Three Cases of Niemann Pick's Disease in Children, Arch. Dis. Childhood **34**:406, 1959.
Foulk, W. T., and Coauthors: Constitutional Hepatic Dysfunction (Gilbert's Disease): Its Natural History and Related Syndromes, Medicine **38**:25, 1959.
Fowler, M.: A Case of Arthrogryposis Multiplex Congenita With Lesions in the Nervous System, Arch. Dis. Childhood **34**:505, 1959.
Fox, A. S.: Genetic Determination of Sex-Specific Antigens, J. Nat. Cancer Inst. **23**:1297, 1959.
Fox, S. R., Jr.: Benign Familial Icterus: A Report of Three Cases, Ann. Int. Med. **50**:115, 1959.
Foxon, G. E. H.: Some Possible Causes of Congenital Heart Malformation, Brit. Heart J. **21**:51, 1959.

VOL. 12 196

Fraccaro, M., Kaijser, K., and Lindsten, J.: Chromosome Complement in Gonadal Dysgenesis (Turner's Syndrome), Lancet **1**:886, 1959.
Fraccaro, M., Kaijser, K., and Lindsten, J.: Chromosome Complement in Parents of Patients With Gonadal Dysgenesis (Turner's Syndrome), Lancet **2**:1090, 1959.
Frank, J., and Piper, P. G.: Congenital Pulmonary Cystic Lymphangiectasis, J.A.M.A. **171**:1094, 1959.
Fraser, D., Leeming, J. M., Cerwenka, E. A., and Kenyeres, K.: Studies of the Pathogenesis of the High Renal Clearance of Phosphate in Hypophosphatemic Vitamin D–Refractory Rickets of the Simple Type (Abstract), A.M.A. J. Dis. Child. **98**:586, 1959.
Fraser, G. R., Harris, H., and Robson, E. B.: A New Genetically Determined Plasma-Protein in Man, Lancet **1**:1023, 1959.
Frayer, W. C., and Blodi, F. C.: The Lattice Type of Familial Corneal Degeneration. A Histopathologic Study, A.M.A. Arch. Ophth. **61**:712, 1959.
Freire-Maia, N., Zuelce-Salgado, A., and Koehler, R. Amundsen: Hereditary Bone Aplasias and Hypoplasias of the Upper Extremities, Acta genet. **9**:33, 1959.
Friberg, L., Kaij, L., Dencker, S. J., and Jonsson, E.: Smoking Habits of Monozygotic and Dizygotic Twins, Brit. M. J. **1**:1090, 1959.
Friedlander, W. J.: Epilepsy, Am. J. Psychol. **1**:623, 1959.
Furman, B.: National Tabulation of Malformations at Birth, New York Times, Oct. 18, 1959. Reprinted, J. Hered. **50**:154, 1959.

Gailitis, R. J., and Schreiber, W.: Idiopathic Hyperlipemia. Special Reference to Abdominal and Coronary Symptoms, A.M.A. Arch. Surg. **79**:40, 1959.
Gajdusek, D. C., and Zigas, V.: Kuru: Clinical, Pathological and Epidemiological Study of an Acute Progressive Degenerative Disease of the Central Nervous System Among Natives of the Eastern Highlands of New Guinea, Am. J. Med. **26**:442, 1959.
Galton, M., and Benirischke, K.: Forty Six Chromosomes in an Ovarian Teratoma, Lancet **2**:761, 1959.
Gans, F., and Ser, J.: Normal Pregnancy and Delivery in Female Pseudohermaphroditism, Acta endocrinol. **30**:424, 1959.
Gardner, D. L.: Familial Canine Chondrodystrophia Foetalis (Achondroplasia), J. Path. & Bact. **77**:243, 1959.
Gardner, L. I., and Migeon, C. J.: Unusual Plasma 17-Ketosteroid Pattern in a Boy With Congenital Adrenal Hyperplasia and Periodic Fever, J. Clin. Endocrinol. **19**:266, 1959.
Gardner, L. I., Rosenthal, I. M., and Feinberg, R. J.: Genetic Aspects of Pediatric Endocrinology, Summary of a Round Table, Pediatrics **24**:330, 1959.
Garrett, G., Hay, W. J., and Rickards, A. G.: Familial Cardiomegaly, J. Clin. Path. **12**:355, 1959.
Garriga, S., and Corsby, W. H.: The Incidence of Leukemia in Families of Patients With Hypoplasia of the Marrow, Blood **14**:1008, 1959.
Garron, L. K.: Cystinosis, Tr. Am. Acad. Ophth. **63**:99, 1959.
Gartler, S. M.: A Metabolic Investigation of Urinary Beta-Aminoisobutyric Acid Excretion in Man, Arch. Biochem. **80**:400, 1959.
Geiser, M., and Buri, P.: Congenital Dislocation of the Hip in Identical Twins, J. Bone & Joint Surg. **41B**:314, 1959.
Genecin, A.: Chronic Pericardial Effusion in Brothers, With a Note on Cholesterol Pericarditis, Am. J. Med. **26**:496, 1959.
Geraci, C. L.: Congenital Absence of the Gallbladder. Diagnosis by Operative Cholangiography, A.M.A. Arch. Surg. **78**:437, 1959.
Gerald, P. S., and George, P.: Second Spectroscopically Abnormal Methemoglobin Associated With Hereditary Cyanosis, Science **129**:383, 1959.
Ghadimi, H., and Shwachman, H.: A Screening Test for Aminoaciduria, New England J. Med. **261**:998, 1959.
Gibbs, N. K., and Woolf, L. I.: Tests for Phenylketonuria, Brit. M. J. **2**:532, 1959.
Giblett, E. R., and Chase, J.: Js^a, A "New" Red-Cell Antigen Found in Negroes; Evidence for an Eleventh Blood Group System, Brit. J. Haemat. **5**:319, 1959.
Giblett, E. R., Hickman, C. G., and Smithies, O.: Serum Transferrins, Nature, London **183**:1589, 1959.
Gibson, D., and Frank, H. F.: Dual Occurrences of Mongolism in Two Sibships, Am. J. Ment. Deficiency **63**:618, 1959.
Gill, E. G., and Harris, R. B.: Congenital Microphthalmos With Cyst Formation, Virginia M. Month. **86**:33, 1959.
Giller, H., and Kaufmann, W. C.: Ocular Lesions in Xeroderma Pigmentosum, A.M.A. Arch. Ophth. **62**:130, 1959.
Gillespie, J. E. O., and Coauthors: A Haemoglobin With Unusual Alkaline-Denaturing Properties in a Turkish-Cypriot Woman, Nature, London **184**:1876, 1959.
Gillett, R. L.: Primary Myoglobinuria, New England J. Med. **260**:1156, 1959.
Gilon, E., Ramat, B., and Sheba, C.: Multiple Hemangiomata Associated With Thrombocytopenia: Remarks on the Pathogenesis of the Thrombocytopenia in this Syndrome, Blood **14**:74, 1959.

Gleditsch, E.: Medionecrosis of the Aorta in Marfan's Syndrome, Acta med. scandinav. **164**:445, 1959.
Glotzer, S.: Myocardial Infarction in the Negro, New York J. Med. **59**:2721, 1959.
Gluck, L.: A Patch Test for Chloride in Sweat as a Simple Screening Method for Detecting Cystic Fibrosis of Pancreas; Preliminary Report, Pediatrics **23**:731, 1959.
Glynn, A. A., Glynn, L. E., and Holborow, E. J.: Secretion of Blood-Group Substances in Rheumatic Fever: A Genetic Requirement for Susceptibility? Brit. M. J. **2**:266, 1959.
Gold, E. R., Tovey, G. H., Benney, W. E., and Lewis, F. J. W.: Changes in the Group A Antigen in a Case of Leukaemia, Nature, London **183**:892, 1959.
Goldberg, A.: Acute Intermittent Prophyria: A Study of 50 Cases, Quart. J. Med. **28**:183, 1959.
Goldberg, E. E., and Pittman, D. R.: Cold Sensitivity Syndrome, Ann. Int. Med. **50**:505, 1959.
Golden, R. L., and Lakim, H.: The "Forme Fruste" in Marfan's Syndrome, New England J. Med. **260**:797, 1959.
Goldman, R., and Haberfelde, G. C.: Hereditary Nephritis: Report of a Kindred, New England J. Med. **261**:734, 1959.
Gómez, G., Esguerra and Coauthors: Familial Pulmonary Alveolar Microlithiasis: Four Cases From Colombia, S. A.: Is Microlithiasis Also an Environmental Disease? Radiology **72**:550, 1959.
Goodman, H. O., and Herndon, C. N.: Genetic Factors in the Etiology of Mental Retardation Internat. Rec. Med. **172**:61, 1959.
Gordin, R., and Enari, T.-M.: Lactic Acid Dehydrogenase in Vitamin B_{12} Deficiency. Genuine Pernicious Anaemia and Pernicious Tapeworm Anaemia, Acta haemat. **21**:16, 1959.
Gordon, A. M.: The Marfan Syndrome: A Study of Five Generations in a Kentucky Family, J. Kentucky M. A. **57**:1511, 1959.
Gordon, H.: Craniostenosis, Brit. M. J. **2**:792, 1959.
Gorham, G. W., and Merselis, J. G., Jr.: Kartagener's Triad: A Family Study, Bull. Johns Hopkins Hosp. **104**:11, 1959.
Graham, G. G., Downs, J. W., and Kahn, A., Jr.: Acute Intermittent Porphyria, Ann. Surg. **25**:135, 1959.
Graham, J. B.: Hereditary Chronic Kidney Disease, Am. J. Human Genet. **11**:333, 1959.
Graham, J. B.: The Inheritance of "Vascular Hemophilia": A New and Interesting Problem in Human Genetics, J. M. Educ. **34**:385, 1959.
Graham, J. B., McFalls, V. W., and Winters, R. W.: Familial Hypophosphatemia With Vitamin D–Resistant Rickets. II. Three Additional Kindreds of the Sex-Linked Dominant Type With a Genetic Analysis of Four Such Families, Am. J. Human Genet. **11**:311, 1959.
Grebe, H.: Erblicher Zwergwuchs, Ergebn. inn. Med. Kinderh. **12**:343, 1959.
Green, D. E., and Järnefelt, J.: Enzymes and Biological Organization, Perspectives Biol. & Med. **2**:163, 1959.
Green, M. C., and Dickie, M. M.: Linkage Map of the Mouse, J. Hered. **50**:3, 1959.
Greenberg, R. E., and Gardner, L. I.: Phaeochromocytoma in Father and Son: Report of the Eighth Known Affected Kindred, J. Clin. Endocrinol. **19**:351, 1959.
Greenwald, J. C., and Fenton, A. N.: Gaucher's Disease and Pregnancy. Report of Three Cases, Obst. & Gynec. **14**:79, 1959.
Greulich, W. W.: Value of X-ray Films of Hand and Wrist in Human Identification, Science **131**:155, 1959.
Grobin, W.: Differences in Incidence of Internal Disease in the Two Sexes, Canad. M.A.J. **80**:991, 1959.
Gross, J. B., and Coauthors: Whipple's Disease; Report of Four Cases, Including Two in Brothers, With Observations on Pathologic Physiology, Diagnosis, and Treatment, Gastroenterology **36**:65, 1959.
Grumbach, M. M., Morishima, A., and Chu, E. H. Y.: On the Sex Chromatin and the Sex Chromosomes in Sexual Anomalies of Man: Relation to Origin of the Sex Chromatin, Abstract for 1st International Congress of Endocrinology, Copenhagen, July, 1960.
Guard, H. R.: A New Technic for Differential Staining of the Sex Chromatin, and the Determination of its Incidence in Exfoliated Vaginal Epithelial Cells, Am. J. Clin. Path. **32**:145, 1959.
Guillard, J., Laumonier, R., Seyer, J., and Boulet, R.: Une observation familiale de syndrome de Peutz-Jeghers, Arch. mal. app. digest. **48**:165, 1959.
Guravich, J. L.: Familial Hypercholesteremic Xanthomatosis: A Preliminary Report. I. Clinical, Electrocardiographic and Laboratory Considerations, Am. J. Med. **26**:8, 1959.
Gutman, A., and Leffkowitz, M.: Tuberous Sclerosis Associated With Spontaneous Hypoglycemia, Brit. M. J. **2**:1065, 1959.
Gutman, A. B., Yü, T. F., and Berger, L.: Tubular Secretion of Urate in Man, J. Clin. Invest. **38**:1778, 1959.

Haahti, E.: Effect of Insulin in a Case of Essential Hyperlipemia, Scandinav. J. Clin. & Lab. Invest. **11**:305, 1959.
Haber, H.: Miescher's Elastoma (Elastoma Intrapapillare Perforans Verniciforme), Brit. J. Dermat. **71**:85, 1959.

VOL. 12 1960

Haddad, H. M., and Wilkins, L.: Congenital Anomalies Associated With Gonadal Aplasia, Review of 55 Cases, Pediatrics **23**:885, 1959.
Hadlow, W. J.: Myopathies of Livestock, Lab. Invest. **8**:1478, 1959.
Haenszel, W.: Some Problems in the Estimation of Familial Risks of Disease, J. Nat. Cancer Inst. **23**:487, 1959.
Haga, H.: Studies on Natural Selection in ABO Blood Groups, With Special Reference to the Influence of Environmental Changes Upon the Selective Pressure Due to Maternal-Fetal Incompatibility, Jap. J. Human Genet. **4**:1, 1959.
Hallgren, B., and Sjögren, T.: A Clinical and Genetico-Statistical Study of Schizophrenia and Low-Grade Mental Deficiency in a Large Swedish Rural Population, Acta psychiat. et neurol. scandinav. **35**:suppl. 140:1-65, 1959.
Hallman, N., and Hjelt, L.: Congenital Nephrotic Syndrome, J. Pediat. **55**:152, 1959.
Harboe, M.: A New Haemagglutinating Substance in the Gm System, Anti-Gm, Nature, London **183**:1468, 1959.
Harboe, M.: A New Hemagglutinating Substance in the Gm System, Anti-Gm^b, Acta path. et. microbiol. scandinav. **47**:191, 1959.
Harboe, M.: Quantitative Studies on the Hemagglutination Inhibition Reaction for Determination of the Gm Types, Acta path. et microbiol. scandinav. **47**:199, 1959.
Harboe, M., and Lundevall, J.: A New Type in the Gm System, Acta path. et microbiol. scandinav. **45**:357, 1959.
Hardin, C. A.: Ruptured Abdominal Aneurysm Occurring in Marfan's Syndrome. Attempted Repair With the Use of a Nylon Prosthesis, New England J. Med. **260**:821, 1959.
Harnden, D. G., and Armstrong, C. N.: The Chromosomes of a True Hermaphrodite, Brit. M. J. **2**:1287, 1959.
Harnden, D. G., Briggs, J. H., and Stewart, J. S. S.: Nuclear Chromatin of Anencephalic Foetuses, Lancet **2**:126, 1959.
Harnischfeger, W. W.: Hereditary Occurrence of the Pre-Excitation (Wolff-Parkinson-White) Syndrome With Re-entry Mechanism and Concealed Conduction, Circulation **19**:28, 1959.
Harris, H., Penrose, L. S., and Thomas, D. H. H.: Cystathioninuria, Ann. Human Genet. **23**:442, 1959.
Harris, H., and Robson, E. B.: A Genetical Study of Ethanolamine Phosphate Excretion in Hypophosphatasia, Ann. Human Genet. **23**:421, 1959.
Harris, H., and Whittaker, M.: Differential Response of Human Serum Cholinesterase Types to an Inhibitor in Potato, Nature, London **183**:1808, 1959.
Hartigan, J. D., and Gurnett, T. J.: Favism—Report of a Case, J.A.M.A. **171**:299, 1959.
Hashimoto, K., and Matsuura, F.: Two Haemoglobins in Chum Salmon, Nature, London **184**:1418, 1959.
Hatch, J. L.: Hereditary Alkaptonuria With Ochronosis, A.M.A. Arch. Ophth. **62**:575, 1959.
Healey, L. A., Magid, G. J., and Decker, J. L.: Uric Acid Retention Due to Hydrochlorothiazide, New England J. Med. **261**:1358, 1959.
Hedenberg, F.: Infantile Agranulocytosis of Probably Congenital Origin, Acta paediat. **48**:77, 1959.
Heierli-Forrer, E.: Zur Klinik und Genetik der hereditären papulosen Palmoplantarkeratosen, Dermatologica **119**:309, 1959.
Hellman, E., and Davoodzadeh, N.: Congenital Spherocytosis, Obst. & Gynec. **13**:92, 1959.
Henderson, A. B., Crockett, E. J., and Wright, C. H.: Effect of Carbonic Anhydrase Inhibitors on the Course of Sickle-Cell Disease, A.M.A. Arch. Int. Med. **104**:68, 1959.
Henderson, J. W.: Enzymatic Zonulolysis: A New Approach to the Surgery of Cataract, Proc. Staff Meet. Mayo Clin. **34**:478, 1959.
Henley, W. L.: Hypogammaglobulinemia and Hypergammaglobulinemia, J. Mount Sinai Hosp. **26**:1038, 1959.
Henricson, B., and Olsson, S.-E.: Hereditary Acetabular Dysplasia in German Shepherd Dogs, J. Am. Vet. M. A. **135**:207, 1959.
Hermansky, F., and Pudlak, P.: Albinism Associated With Hemorrhagic Diathesis and Unusual Pigmented Reticular Cells in the Bone Marrow: Report of 2 Cases With Histochemical Studies, Blood **14**:162, 1959.
Hertel, A., and Zanalda, A.: Osservazioni e considerazioni sulle condizioni dentarie e dei tessuti paradentali nel mongolismo, Folia hered. et path. **8**:375, 1959.
Hill, R. L., and Schwartz, H. C.: A Chemical Abnormality in Hemoglobin G, Nature, London **184**:641, 1959.
Hillenius, L.: Intrathoracic Meningocoele, Acta med. scandinav. **163**:15, 1959.
Hird, W. E., and Hortenstine, C. B.: Familial Esophageal Epiphrenal Diverticula, J.A.M.A. **171**:1924, 1959.
Hirschhorn, K., and Wilkinson, C. F., Jr.: The Mode of Inheritance in Essential Familial Hypercholesterolemia, Am. J. Med. **26**:60, 1959.
Hitch, J. M., and Lund, H. Z.: Elastosis Perforans Serpiginosa, A.M.A. Arch. Dermat. **79**:407, 1959.
Hitzig, W. H., Biró, Z., Bosch, H., and Huser, H. J.: Agammaglobulinämie und Alymphocytose mit Schwund des lymphatischen Gewebes, Helvet. paediat. acta **13**:551, 1958.

OL.
12
960

Hoagland, M. B.: Nucleic Acids and Proteins, Scient. Am. **201**:55, 1959.
Hodgson, C. H., Burchell, H. B., Good, C. A., and Clagett, O. T.: Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Fistula, New England J. Med. **261**:625, 1959.
Hollander, W. F., and Gowen, J. W.: A Single-Gene Antagonism Between Mother and Fetus in the Mouse, Proc. Soc. Exper. Biol. & Med. **101**:425, 1959.
Holman, R. L., Blanc, W. A., and Andersen, D.: Decreased Aortic Atherosclerosis in Cystic Fibrosis of the Pancreas, Pediatrics **24**:34, 1959.
Horn, D., Courts, F. A., Taylor, R. M., and Solomon, E. S.: Cigarette Smoking Among High School Students, Am. J. Pub. Health **49**:1497, 1959.
Horwitz, H., Bassen, F. A., and Simon, N.: Haemophilic Pseudotumour of the Pelvis, Brit. J. Radiol. **32**:51, 1959.
Hougie, C., and Glover, H. M.: The Hemophiloid States; the Practical Application of Present-Day Concepts of Blood Coagulation to Diagnosis and Treatment, A.M.A. Arch. Int. Med. **103**:239, 1959.
Howarth, B.: Coxa Plana, Arch. Pediat. **76**:1, 1959.
Hsia, D. Y.-Y: Birth Weight in Cystic Fibrosis of the Pancreas, Ann. Human Genet. **23**:289, 1959.
Hsia, D. Y.-Y., and Kot, E. G.: Detection of Heterozygous Carriers in Glycogen Storage Disease of the Liver (von Gierke's Disease), Nature, London **183**:1331, 1959.
Hsia, D. Y.-Y., Naylor, J., and Bigler, J. A.: Gaucher's Disease; Report of Two Cases in Father and Son and Review of the Literature, New England J. Med. **261**:164, 1959.
Huang, I., Hugh-Jones, K., and Hsia, D. Y.-Y.: Studies on the Heterozygous Carrier in Galactosemia, J. Lab. & Clin. Med. **54**:585, 1959.
Hughes, D. T. D.: The Clinical and Pathological Background of Two Cases of Oxalosis, J. Clin. Path. **12**:498, 1959.
Hummel, K. P.: Developmental Anomalies in Mice Resulting From Action of the Gene, Disorganization, a Semi-Dominant Lethal, Pediatrics **23**:212, 1959.
Hummel, K. P., and Chapman, D. B.: Visceral Inversion and Associated Anomalies in the Mouse, J. Hered. **50**:9, 1959.
Hungerford, D. A., Donnelly, A. J., Nowell, P. C., and Beck, S.: The Constitution of a Human Phenotypic Intersex, Am. J. Human Genet. **11**:215, 1959.
Hunt, J. A.: Identity of the Alpha-Chains of Adult and Foetal Haemoglobins, Nature, London **183**:1373, 1959.
Hunt, J. A., and Ingram, V. M.: Human Haemoglobin E; the Chemical Effect of Gene Mutation, Nature, London **184**:870, 1959.
Hunt, J. A., and Ingram, V. M.: A Terminal Peptide Sequence of Human Haemoglobin? Nature, London **184**:640, 1959.
Hunt, J. A., and Lehmann, H.: Haemoglobin "Bart's" a Foetal Haemoglobin Without Alpha-Chains, Nature, London **184**:872, 1959.
Hurwitt, E. S., and Lebendiger, A.: Ectopia Cordis in a Twin, A.M.A. Arch. Surg. **78**:197, 1959.
Hutchings, J. J.: Complete Sex Reversal: A Case Report, J. Clin. Endocrinol. **19**:375, 1959.
Hyatt, H. W.: Hemolytic Disease of the Newborn in a Pair of Monzygotic Twins Due to Sensitization to Blood Factors hr′, Exper. Med. & Surg. **17**:262, 1959.

Ingram, V. M.: Chemistry of the Abnormal Human Haemoglobins, Brit. M. Bull. **15**:27, 1959.
Ingram, V. M.: Separation of the Peptide Chains of Human Globin, Nature, London **183**:1795, 1959.
Ingram, V. M., and Stretton, H. O. W.: Genetic Bases of the Thalassaemic Diseases, Nature, London **184**:1903, 1959.
Innes, J. R. M.: "Inherited Dysplasia" of the Hip-Joint in Dogs and Rabbits, Lab. Invest. **8**:1170, 1959.
Ipsen, J.: Differences in Primary and Secondary Immunization of Inbred Mice Strains, J. Immunol. **83**:448, 1959.
Israels, L. G., Suderman, H. J., and Ritzmann, S. E.: Hyperbilirubinemia Due to an Alternate Path of Bilirubin Production, Am. J. Med. **27**:693, 1959.
Isselbacher, K. J.: Galactose Metabolism and Galactosemia, Am. J. Med. **26**:715, 1959.
Itano, H. A., and Robinson, E.: Formation of Normal and Doubly Abnormal Haemoglobins by Recombination of Haemoglobin I With S and C, Nature, London **183**:1799, 1959.
Itano, H. A., and Robinson, E.: Properties and Inheritance of Haemoglobin by Asymmetric Recombination, Nature, London **184**:1468, 1959.
Ivemark, B. I., Oldfelt, V., and Zetterström, R.: Familial Dysplasia of Kidneys, Liver and Pancreas. A Probably Genetically Determined Syndrome, Acta paediat. **48**:1, 1959.

Jackson, C. E.: The Association of Peptic Ulcer With Hereditary Hyperparathyroidism, Gastroenterology **37**:35, 1959.
Jackson, C. E., and Gay, B. C.: Inheritance of Gall-Bladder Disease, Surgery **46**:853, 1959.
Jacobs, P. A., Baikie, A. G., Court Brown, W. M., and Strong, J. A.: The Somatic Chromosomes in Mongolism, Lancet **1**:710, 1959.

VOL. 12 1960

Jacobs, P. A., and Coauthors: Chromosomal Sex in the Syndrome of Testicular Feminisation, Lancet **2**:591, 1959.
Jacobs, P. A., and Coauthors: Evidence for the Existence of the Human "Super Female," Lancet **2**:423, 1959.
Jacobs, P. A., and Coauthors: Use of the Term "Superfemale," Lancet **2**:1145, 1959.
Jacobs, P. A., and Keay, A. J.: Somatic Chromosomes in Bonnevie-Ullrich Syndrome, Lancet **2**:732, 1959.
Jacobs, P. A., and Strong, J. A.: A Case of Human Intersexuality Having a Possible XXY Sex-Determining Mechanism, Nature, London **183**:302, 1959.
Jacobs, P. H., Shafer, J. C., and Higdon, R. S.: Congenital Branchiogenous Anomalies, J.A.M.A. **169**:442, 1959.
Jailer, J. W., Ulick, S., and Lieberman, S.: Aldosterone and Hydrocortisone Secretion Rates in Patients With the Salt-Losing Form of Congenital Adrenal Hyperplasia, Tr. A. Am. Physicians **72**:149, 1959.
Javid, J., Fischer, D. S., and Spaet, T. H.: Inability of Haptoglobin to Bind Myoglobin, Blood **14**:683, 1959.
Javid, J., Horowitz, H. I., Sanders, A. R., and Spaet, T. H.: Idiopathic Paroxysmal Myoglobinuria, A.M.A. Arch. Int. Med. **104**:628, 1959.
Jehle, H.: Amino Acid Sequence Selection in Protein Synthesis, Proc. Nat. Acad. Sc. **45**:1360, 1959.
Jenne, J. W.: Studies of Human Metabolism of Isoniazid Using an Intravenous Fall-off Technique and a Chemical Method, Clin. Res. **7**:393, 1959.
Johnson, O. N.: Hereditary Dentinogenesis Imperfecta, J. Pediat. **54**:6, 1959.
Jones, B., and Klingberg, W. G.: Hemoglobin S; Hereditary Spherocytosis; Two Case Reports, J. Pediat. **54**:375, 1959.
Jones, R. T., Schroeder, W. A., Balog, J. E., and Vinograd, J. R.: Gross Structure of Hemoglobin H, J. Am. Chem. Soc. **81**:3161, 1959.
Jones, T. C.: Equine Incoordination (Ataxia of Foals, "Wobbles"), Lab. Invest. **8**:1266, 1959.
Jones, R. V., McSwiney, R. R., and Brooks, R. V.: Periodic Paralysis; Sodium Metabolism and Aldosterone Output in 2 Cases, Lancet **1**:177, 1959.
Jonxis, J. H. P., and Delafresnaye, J. S., editors: Abnormal Haemoglobins: A Symposium, Oxford, 1959, Blackwell Scientific Publications.
Jorpes, J. E.: V. Willebrand's Disease and Its Treatment With a Specific Plasma Fraction. Scot. M. J. **4**:269, 1959.
Joysey, V. C., Goodwin, R. F. W., and Coombs, R. R. A.: The Blood Groups of the Pig. VI. Red Cell Antigens Other Than the A-O System, J. Comp. Path. & Therap. **69**:29, 1959.
Julkunen, H., and Tiilikainen, A.: Importance of an Increased Gamma Globulin Level in the Determination of Gm Groups in Collagen Diseases, Ann. Rheumat. Dis. **18**:318, 1959.

Kähler, H. J.: Die Myoglobinurien, Ergebn. inn. Med. Kinderh. **11**:1, 1959.
Kaelin, A.: Méthods d'estimation et tests dans les répartitions multinomiales, avec application aux données de Taillard et Prader concernant l'intersexualité, J. génét. humaine **8**:134, 1959.
Kallmann, F. J.: Heredity and Eugenics, Am. J. Psychiat. **115**:586, 1959.
Kallmann, F. J., and Rainer, J. D.: Genetics and Demography, *in* Hauser, P. M., and Duncan, O. D., editors: The Study of Population, Chicago, 1959, University of Chicago Press.
Kalow, W.: The Distribution, Destruction and Elimination of Muscle Relaxants, Anaesthesiology **20**:505, 1959.
Kalow, W., and Gunn, D. R.: Some Statistical Data on Atypical Cholinesterase of Human Serum, Ann. Human Genet. **23**:238, 1959.
Kalter, H., and Warkany, J.: Experimental Production of Congenital Malformations in Mammals by Metabolic Procedures, Physiol. Rev. **39**:69, 1959.
Kantor, S. Z., and Arbesman, C. E.: Serologic Studies on Favism, J. Allergy **30**:116, 1959.
Kaplan, I. I.: Genetic Effects in Children and Grandchildren of Women Treated for Infertility and Sterility by Roentgen Therapy; Report of a Study of Thirty-Three Years, Radiology **72**:518, 1959.
Karr, W. J., Jr.: Fabry's Disease (Angiokeratoma Corporis Diffusum Universale). An Unusual Syndrome With Multisystem Involvement and Unique Skin Manifestations, Am. J. Med. **27**:829, 1959.
Katzen, M., and Coauthors: The Peutz Syndrome (Report of an Affected Family), South African M. J. **33**:492, 1959.
Katzuni, E., and Sandbank, U.: Oxalosis, Arch. Dis. Childhood **34**:60, 1959.
Kaufman, H. E., and Thomas, L. B.: Vitreous Opacities Diagnostic of Familial Primary Amyloidosis, New England J. Med. **261**:1267, 1959.
Kaufman, R. P., and Barry, P. E.: Rhabdomyolysis With Myoglobinuria; Report of a Case, New England J. Med. **260**:430, 1959.
Keen, H., and Rose, G.: The Nature of Essential Hypertension, Lancet **2**:1028, 1959.
Keltz, H., and Comstock, G. W.: Serum Globulin Levels in Whites and Negroes, New England J. Med. **260**:1268, 1959.
Kendig, E. L., Peacock, R. L., and Ryburn, S.: Sarcoidosis, New England J. Med. **260**:962 1959.

Kerlinger, F. N.: Correlation, Science **130**:1366, 1959.
Khosrovani, H.: Malformations of the Hands and Feet (Ectrodactylia) Through Five Successive Generations of a Large Vaudois Family, J. génét. humaine **8**:1, 1959.
Kilburn, K. H., Eagan, J. T., and Heyman, A.: Cardiopulmonary Insufficiency Associated With Myotonic Dystrophy, Am. J. Med. **26**:929, 1959.
Kilburn, K. H., Eagan, J. T., Sieker, H. O., and Heyman, A.: Cardiopulmonary Insufficiency in Myotonic and Progressive Muscular Dystrophy, New England J. Med. **261**:1089, 1959.
Kirk, R. L., Vos, G. H., and Kelsall, G. A.: Rh Genotype of the Father and Severity of Haemolytic Disease of the Newborn, Brit. J. Haemat. **5**:158, 1959.
Kirkman, H. N.: Characteristics of Glucose-6-Phosphate Dehydrogenase from Normal and Primaquine-Sensitive Erythrocytes, Nature, London **184**:1291, 1959.
Kirkman, H. N., and Bynum, E.: Enzymic Evidence of a Galactosemic Trait in Parents of Galactosemic Children, Ann. Human Genet. **23**:117, 1959.
Kitchin, F. D., and Coauthors: P.T.C. Taste Response and Thyroid Disease, Brit. M. J. **1**:1069, 1959.
Kjer, Poul: Infantile Optic Atrophy With Dominant Mode of Inheritance, Opera ex Domo Biol. Hered. Humanae Univ. Hafniensis **42**:1-146, 1959.
Kjølbye, J. E., and Nielsen, E. L.: ABO Blood Groups in Cholelithiasis, Acta genet. **9**:213, 1959.
Klaus, S. N., and Brunsting, L. A.: Melkersson's Syndrome (Persistent Swelling of the Face, Recurrent Facial Paralysis, and Lingua Plicata): Report of Case, Proc. Staff Meet. Mayo Clin. **34**:365, 1959.
Klinker, W., and Schnyder, U. W.: Über die Bedeutung der Genetik für die Klassifizierung der Allergien, Internat. Arch. Allergy **15**:360, 1959.
Kluge, W.: Acrocephalosyndactyly or Apert's Syndrome, Report of a Case, M. Proc. **5**:426, 1959.
Klunker, W.: A Genealogical Tree of a Family Affected With Simple Epidermolysis Bullosa (Koebner's Disease), J. génét. humaine **8**:72, 1959.
Knight, R. A., Selin, M. J., and Harris, H. W.: Genetic Factors Influencing Isoniazid Blood Levels in Humans, Tr. Conf. Chemotherap. Tuberc. (VA-Armed Forces) **18**:52, 1959.
Knights, E. M., Jr., Brush, J. S., and Schroeder, J.: Simplified Screening Test for Cystic Fibrosis of the Pancreas, J.A.M.A. **169**:1279, 1959.
Kobayashi, N.: Acid Mucopolysaccharide Granules in the Glomerular Epithelium in Gargoylism, Am. J. Path. **35**:591, 1959.
Koch, E.: Die erbliche Erwachsenen-Mucoviscidosis und ihre Beziehungen zur Ulkuskrankheit, Deutsche med. Wchnschr. **84**:1773, 1959.
Koch, G.: Genetics of Microcephaly in Man, Acta genet. med. et gemel. **8**:75, 1959.
Kohn, P. M., and Prozan, G. B.: Hyperuricemia—Relation to Hypercholesterolemia and Acute Myocardial Infarction, J.A.M.A. **170**:1909, 1959.
Koller, F., Vogel-Meng, J., and Steiner, E.: Physiology and Pathology of Blood Coagulation, A Review of the Literature (First Series 1959), Thromb. et Diath. Haemorrh. No. 4:101, 1959.
Kooij, R., and Venter, J.: Atrophodermia Vermiculata With Unusual Localisation and Associated Congenital Anomalies, Dermatologia **118**:161, 1959.
Koprowski, H.: Importance of Genetics of Viruses in Medical Research J. M. Educ. **34**:335, 1959.
Korein, J., Coddon, D. R., and Mowrey, F. H.: The Clinical Syndrome of Paroxysmal Paralytic Myoglobinuria, Neurology **9**:767, 1959.
Kortekangas, A. E., and Coauthors: A Second Family With the Red Cell Antigen P^k, Vox Sang. **4**:337, 1959.
Kosin, I. L., and Ishizaki, N.: Incidence of Sex Chromatin in Gallus domesticus (Abstract), Science **130**:43, 1959.
Kravitz, D.: Lens Surgery in Marfan's Syndrome, A.M.A. Arch. Ophth. **62**:764, 1959.
Krivit, W., and Good, R. A.: Aldrich's Syndrome (Thrombocytopenia, Eczema, and Infection in Infants), A.M.A. J. Dis. Child. **97**:137, 1959.
Krivit, W., Goodlin, R., Ziegler, N., and Lienke, R.: Foetomaternal Transfusion as a Cause of Neonatal Anaemia, Arch. Dis. Childhood **34**:471, 1959.
Kunkel, H. G.: Immunologic Aspects of Rheumatoid Arthritis, J. CHRON. DIS. **10**:418, 1959.
Kutscher, A. H., Zegarelli, E. V., Rankow, R. M., and Mercandante, J. L.: Peutz-Jeghers Syndrome: Follow-ups on Patients Reported on in the Literature, Am. J. M. Sc. **238**:180, 1959.

LaDu, B. N.: The Importance of Early Diagnosis and Treatment of Phenylketonuria, Ann. Int. Med. **51**:1427, 1959.
Lalezari, P., and Spaet, T. H.: Studies on the Genetics of Leukocyte Antigens, Blood **14**:748, 1959.
Lang, H. A.: Retinal Degeneration and Nerve Deafness, Brit. M. J. **2**:1096, 1959.
Laplane, R., Lasfargues, G., and Debray, P.: Essai de classification génétique des ostéogenèses imparfaites, Presse méd. **67**:893, 1959.
Larner, J., and Villar-Palasi, C.: Enzymes in a Glycogen Storage Myopathy, Proc. Nat. Acad. Sc. **45**:1234, 1959.
Larsson, O., and Leonhardt, T.: Hereditary Hypergammaglobulinaemia and Systemic Lupus Erythematosus, Part I, Acta med. scandinav. **165**:371, 1959.

VOL. 12 196

Laski, B., Donohue, W. L., Uchida, I., and Munn, J. D.: Familial Pulmonary Fibrosis and Its Relationship With the Hamman-Rich Syndrome, A.M.A. J. Dis. Child. **98**:503, 1959.
Lathrop, D. B.: Cystic Disease of the Liver and Kidney, Pediatrics **24**:215, 1959.
Lau, F. Y. K.: Pulmonary Infarction and Atrophy of the Spleen Associated With Sickle-Cell Hemoglobin C Disease, New England J. Med. **260**:907, 1959.
Laurell, C. B.: Determination of the Haptoglobin Group, Scandinav. J. Clin. & Lab. Invest. **11**:18, 1959.
Lawrence, J. S., and Mellinkoff, S. M.: Familial Mediterranean Fever, Tr. A. Am. Physicians **72**:111, 1959.
Layrisse, M., and de Layrisse, Z.: Frequency of the New Blood Group Antigen Js^a Among South American Indians, Nature, London **184**:640, 1959.
Leading Article: Nuclear Sex in Teratomas, Lancet **2**:777, 1959.
Lechner, G. W., and Connolly, P. J.: Benign Neoplasms of the Small Intestine, With a Report of Three Bleeding Benign Tumors of the Jejunum, J.A.M.A. **169**:2003, 1959.
Lederberg, J.: Genes and Antibodies, Science **129**:1649, 1959.
Lederberg, J.: A View of Genetics, Stanford M. Bull. **17**:120, 1959; Science **131**:269, 1960.
Lehmann, H.: Classification and Identification of Human Haemoglobins, Proc. Roy. Soc. Med. **52**:959, 1959.
Lehmann, H.: Inheritance of Human Haemoglobins, Brit. M. Bull. **15**:40, 1959.
Lehmann, H., and Nwokolo, C.: The River Niger as a Barrier in the Spread Eastwards of Haemoglobin C: A Survey of Haemoglobins in the Ibo, Nature, London **183**:1587, 1959.
Lehndorff, H.: Die Endokard-Fibroelastose, Ergebn. inn. Med. Kinderh. **12**:302, 1959.
Lehndorff, H.: The Problem of Endocardial Fibroelastosis, Arch. Pediat. **76**:85, 1959.
Leifheit, E. C., and Smith, E. R. B.: Quantitative Estimation of Isonicotinic Acid Hydrazide and Para-aminosalicylic Acid in Blood Serum, Am. J. Clin. Path. **31**:142, 1959.
Lejeune, J., Gautier, M., and Turpin, R.: Les chromosomes humains en culture de tissus, C. rend. Acad. sc. **248**:602, 1959.
Lejeune, J., Gautier, M., and Turpin, R.: The Chromosomes of Man, Lancet **1**:885, 1959.
Lejeune, J., Gautier, M., and Turpin, R.: Étude des chromosomes somatiques de neuf enfants mongoliens, C. rend. Acad. sc. **248**:1721, 1959.
Lenz, W.: Der Einfluss der Alters der Eltern und der Geburtennummer auf angeborene pathologische Zustande beim Kind, Acta genet. **9**:169, 1959.
Leonard, S. A., and McGuire, F. L.: Phenylketonuria: An Unusual Case, J. Pediat. **54**:210,1959.
Leonhardt, T.: Hereditary Hypergammaglobulinaemia and Systemic Lupus Erythematosus, Part II, Acta med. scandinav. **165**:395, 1959.
Lerman, S.: Chemistry, Heredity and Disease, Am. J. M. Sc. **238**:397, 1959.
Lerman, S.: Enzymatic Factors in Experimental Galactose Cataract, Science **130**:1473, 1959.
Lerman, S.: The Lens in Congenital Galactosemia, A.M.A. Arch. Ophth. **61**:88, 1959.
Le Roux, B. T.: Pulmonary Arteriovenous Fistulae, Quart. J. Med. **28**:1, 1959.
Levin, S., Baens, G. S., and Weinberg, T.: The Heart in Pseudohypertrophic Muscular Dystrophy, J. Pediat. **55**:460, 1959.
Levine, S.: Chronic Familial Neutropenia With Marked Periodontal Lesions, Oral Surg. **12**:310, 1959.
Levitt, J. M.: Hereditary Changes in Skin of the Eyelids, A.M.A. Arch. Ophth. **62**:506, 1959.
Levy, G., and Brewer, R. L.: Pseudoxanthoma Elasticum: Report of a Case, Am. J. Med. **26**:157, 1959.
Lewis, J. H., and Merchant, W. R.: Application of Continuous Flow Electrophoresis to the Study of the Blood Coagulation Proteins, II. The Hemophilias (A and B), J. Clin. Invest. **38**:1924, 1959.
Lichtenstein, B. W., and Rosenbluth, P. R.: Schilder's Disease With Melanoderma, J. Neuropath. & Exper. Neurol. **18**:384, 1959.
Lie-Injo, L. E., Hoo, S. T., and Kho, L. K.: A Case of Haemoglobin E–Thalassaemia Disease Complicated by Pregnancy, Acta haemat. **22**:194, 1959.
Lilienfeld, A. M.: A Methodological Problem in Testing a Recessive Genetic Hypothesis in Human Disease, Am. J. Pub. Health **49**:199, 1959.
Lisan, P., Imbriglia, J., and Likoff, W.: Myocardial Disease Associated With Progressive Muscular Dystrophy (a Report of 2 Cases), Am. Heart J. **57**:913, 1959.
Litin, R. B., and Coauthors: Hypercalciuria in Hepatolenticular Degeneration (Wilson's Disease), Am. J. M. Sc. **238**:614, 1959.
Liu, M. C., and Corlett, K.: A Study of Congenital Heart Defects in Mongolism, Arch. Dis. Childhood **34**:410, 1959.
Lobdell, D. H.: Congenital Absence of the Parathyroid Glands, A.M.A. Arch. Path. **67**:412, 1959.
Loewenthal, L. J. A.: Albinoidism With Epitheliomatosis, Brit. J. Dermat. **71**:37, 1959.
Loewenthal, L. J. A.: Familial Benign Chronic Pemphigus; the Role of Pyogenic Bacteria, A.M.A. Arch. Dermat. **80**:318, 1959.
Lohss, F., and Kallee, E.: Spurennachweis von Albumin durch Analyse von Antigen-Antikörper-praezipitaten, Clin. chim. acta **4**:127, 1959.

Lomas, J. J. P., and Boyle, A. C.: Osteochondrodystrophy (Morquio's Disease) in Three Generations, Lancet **2**:430, 1959.
Lonergan, P., and Robbins, S. L.: Absence of Intracapillary Glomerulosclerosis in the Diabetic Patient With Hemochromatosis, New England J. Med. **260**:367, 1959.
Lother, K.: Familiaeres Vorkommen von Foramina parietalia permagna, Arch. Kinderh. **160**:156, 1959.
Lubowe, I. I.: The Clinical Aspects of Alopecia Areata, Totalis, and Universalis, Ann. New York Acad. Sc. **183**:458, 1959.
Lubs, H. A., Jr., Vilar, O., and Bergenstal, D. M.: Familial Male Pseudohermaphrodism With Labial Testes and Partial Feminization: Endocrine Studies and Genetic Aspects, J. Clin. Endocrinol. **19**:1110, 1959.
Lygren, T.: Hepatolenticular Degeneration (Wilson's Disease) and Juvenile Cirrhosis in the Same Family, Lancet **1**:275, 1959.
Lygren, T., Sörensen, E. W., and Bernhardsen, A.: Hepatolenticular Degeneration (Wilson's Disease): A Case Diagnosed Biochemically Before Clinical Manifestations, Lancet **1**:276, 1959.

McAlpine, S. G.: Haemochromatosis in a Family, and Its Occurrence in Two Women, Brit. M. J. **2**:618, 1959.
McCaslin, F. E., Jr., and Janes, J. M.: The Effect of Strontium Lactate in the Treatment of Osteoporosis, Proc. Staff Meet. Mayo Clin. **34**:329, 1959.
McCleary, J., Brunsting, L. A., and Kennedy, R.: Primary Xanthoma Tuberosum in Children (With Classification of Xanthomas), Pediatrics **23**:67, 1959.
McConaghy, N.: The Use of an Object Sorting Test in Elucidating the Hereditary Factor in Schizophrenia, J. Neurol. Neurosurg. & Psychiat. **22**:243, 1959.
McConnell, R. B.: Secretion of Blood Group Antigens in Gastrointestinal Diseases, Gastroenterologia **92**:103, 1959.
McGirr, E. M., Clement, W. E., Currie, A. R., and Kennedy, J. S.: Impaired Dehalogenase Activity as a Cause of Goitre With Malignant Changes, Scot. M. J. **4**:232, 1959.
McGirr, E. M., Hutchison, J. H., and Clement, W. E.: Sporadic Goitre Due to Dyshormonogenesis: Impaired Utilisation of Trapped Iodine, Scot. M. J. **4**:107, 1959.
McIntyre, P. A., Hahn, R., Conley, C. L., and Glass, B.: Genetic Factors in Predisposition to Pernicious Anemia, Bull. Johns Hopkins Hosp. **104**:309, 1959.
Mack, H. C.: Adult Hypertrophic Pyloric Stenosis, A.M.A. Arch. Int. Med. **104**:574, 1959.
McKee, D. M., and Edgerton, M. T.: The Surgical Treatment of Lymphedema of the Lower Extremities, Plast. & Reconstruct. Surg. **23**:480, 1959.
Mackenzie, D. Y., and Woolf, L. I.: "Maple Syrup Urine Disease," An Inborn Error of the Metabolism of Valine, Leucine, and Isoleucine Associated With Gross Mental Deficiency, Brit. M. J. **1**:90, 1959.
Macklin, M. T.: Inheritance of Retinoblastoma in Ohio, A.M.A. Arch. Ophth. **62**:842, 1959.
Macklin, M. T.: Relative Status of Parity and Genetic Background in Producing Human Breast Cancer, J. Nat. Cancer Inst. **23**:1179, 1959.
McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.
McLachlin, A. D.: Familial Intestinal Polyposis, A.M.A. Arch Surg. **79**:393, 1959.
Mäkelä, O., Eriksson, A. W., and Lehtovaara, R.: On the Inheritance of the Haptoglobin Serum Groups, Acta genet. **9**:149, 1959.
Malawista, S. E., Boies, L. R., and Seides, S. W.: Rheumatoid Arthritis in Liberia, Ann. Rheumat. Dis. **18**:305, 1959.
Mallén, M. S., and Arias, T.: Inheritance of Diego Blood Group in Mexican Indians, Science **130**:164, 1959.
Marder, V. J., and Conley, C. L.: Electrophoresis of Hemoglobin on Agar Gels. Frequency of Hemoglobin D in Negro Population, Bull. Johns Hopkins Hosp. **105**:77, 1959.
Margolis, J.: Ollier's Disease, A.M.A. Arch. Int. Med. **103**:279, 1959.
Markert, C. L., and Hunter, R. L.: The Distribution of Esterases in Mouse Tissues, J. Histochem. & Cytochem. **7**:42, 1959.
Markert, C. L., and Møller, F.: Multiple Forms of Enzymes: Tissue, Ontogenetic, and Species Specific Patterns, Proc. Nat. Acad. Sc. **45**:753, 1959.
Marks, P. A., and Gross, R. T.: Drug Induced Hemolytic Anemias and Congenital Galactosemia, Bull. New York Acad. Med. **35**:433, 1959.
Marks, P. A., and Gross, R. T.: Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency; Evidence of Differences Between Negroes and Caucasians With Respect to This Genetically Determined Trait, J. Clin. Invest. **38**:2253, 1959.
Marks, P. A., Gross, R. T., and Hurwitz, R. E.: Gene Action in Erythrocyte Deficiency of Glucose-6-Phosphate Dehydrogenase: Tissue Enzyme-Levels, Nature, London **183**:1266, 1959.
Markson, L. M., Carnaghan, R. B. A., and Young, G. B.: Familial Cerebellar Degeneration and Atrophy—a Sex Linked Disease Affecting Light Sussex Pullets, J. Comp. Path. & Therap. **69**:223, 1959.

VOL. 12 1960

Maroteaux, P., and Lamy, M.: Les formes pseudoachondroplastiques des dysplasies spondylo-épiphysaires, Presse méd. **67**:383, 1959.
Marshall, D., Saul, G. B., and Sachs, E., Jr.: Tuberous Sclerosis. A Report of 16 Cases in Two Family Trees Revealing Genetic Dominance, New England J. Med. **261**:1102, 1959.
Marshall, J.: Observations on Endocrine Function in Dystrophia Myotonica, Brain **82**:221, 1959.
Martin, W. W., Jr., Kough, R. H., and Branche, G. C., Jr.: Hereditary Spherocytosis-Sicklemia in the Negro; Case Report and Study of a Negro Family Having Multiple Instances of Hereditary Spherocytosis, Blood **14**:688, 1959.
Matsunaga, E.: Further Notes on the Problem of the Occurrence of a Third Type of Human Twins, With a Correction of the Previous Study, Jap. J. Human Genet. **4**:150, 1959.
Matsunaga, E.: Incomplete Dominance of the Gene for Secretion of the Blood Group Antigens in Human Saliva, Jap. J. Human Genet. **4**:173, 1959.
Matsunaga, E., and Ogyn, H.: Genetic Study of Retinoblastoma in a Japanese Population, Jap. J. Human Genet. **4**:156, 1959.
Maudsley, R. H.: Osteochondrodystrophy or Dysplasia Epiphysealis Multiplex? Lancet **2**:616, 1959.
Maumanee, A. E.: The Pathogenesis of Congenital Glaucoma, Am. J. Ophth. **47**:827, 1959.
Meeuwisse, G. W.: An Attempt With STH-Treatment in Chondrodystrophic Dwarfism, Acta paediat. **48**:109, 1959.
Megevand, A.: Visceral Polyposis and Cutaneomucosal Melanin Pigmentation (Peutz Syndrome), Arch. franç. pédiat. **16**:353, 1959.
Meier, H.: A Sex Difference in White Blood Cells of Rats (WR Strain), Nature, London **184**:1082, 1959.
Meier, H., and Yerganian, G. A.: Spontaneous Hereditary Diabetes Mellitus in Chinese Hamster. 1. Pathological Findings, Proc. Soc. Exper. Biol. & Med. **100**:810, 1959.
Mellinkoff, S. M., Halpern, R. M., Frankland, M., and Griepel, M.: Abnormal Urinary Amino Acid Patterns in Acute Intermittent Porphyria, J. Lab. & Clin. Med. **53**:358, 1959.
Melnick, J. C.: Osteopathia Condensans Disseminata (Osteopoikilosis); Study of a Family of 4 Generations, Am. J. Roentgenol. **82**:229, 1959.
Mendlowitz, M., Gitlow, S., and Naftchi, N.: The Cause of Essential Hypertension, Perspectives Biol. & Med. **2**:354, 1959.
Menkes, J. H.: Maple Syrup Disease, Neurology **9**:826, 1959.
Menkes, J. H.: Maple Syrup Disease; Isolation and Identification of Organic Acids in the Urine, Pediatrics **23**:348, 1959.
Mercantini, E. S., and Mopper, C.: Neurilemmoma of the Tongue, A.M.A. Arch. Dermat. **79**:203, 1959.
Meredith, J. H., and Clarkson, T. B.: Tetralogy of Fallot in the Dog., J. Am. Vet. M. A. **135**:326, 1959.
Metaxas, M. N., Metaxas-Bühler, M., Dunsford, I., and Holländer, L.: A Further Example of Anti-Lu^b Together With Data in Support of the Lutheran-Secretor Linkage in Man, Vox. Sang. **4**:298, 1959.
Metz, J.: Hereditary Spherocytosis in the Bantu, South African M. J. **33**:1034, 1959.
Meyer, K., Hoffman, P., Linker, A., Grumbach, M. M., and Sampson, P.: Sulfated Mucopolysaccharides of Urine and Organs in Gargoylism (Hurler's Syndrome). II. Additional Studies, Proc. Soc. Exper. Biol. & Med. **102**:587, 1959.
Milch, R. A.: A Preliminary Note of 47 Cases of Alkaptonuria Occurring in Seven Interrelated Dominican Families, With an Additional Comment on Two Previously Reported Pedigrees, Acta genet. **9**:123, 1959.
Miller, S.: Band-Keratopathy With a Report of a Case of Fanconi's Syndrome With Calcium Deposits in the Cornea, Tr. Ophth. Soc. **78**:59, 1959.
Miller, S. P.: Congenital Deficiency of Proconvertin: A Clinical and Laboratory Report, Blood **14**:1322, 1959.
Millis, J.: The Frequency of Twinning in Poor Chinese in the Maternity Hospital, Singapore, Ann. Human Genet. **23**:171, 1959.
Mills, S. D., and Winkelmann, R. K.: Eczema, Thrombocytopenic Purpura and Recurring Infections. A Familial Disorder With Report of Four Families, A.M.A. Arch. Dermat. **79**:466, 1959.
Milne, M. D., Crawford, M. A., Girão, C. B., and Loughridge, L.: The Metabolic Abnormality of Hartnup Disease, Biochem. J. **72**:30P, 1959.
Mitchell, R. G., and Rhaney, K.: Congenital Adrenal Hypoplasia in Siblings, Lancet **1**:488, 1959.
Mitoma, C., and Coauthors: Improvements in Methods for Measuring Hydroxyproline, J. Lab. & Clin. Med. **53**:970, 1959.
Mittwoch, U.: Abnormal Lymphocytes in Gargoylism, Brit. J. Haemat. **5**:365, 1959.
Mitus, W. J., Mednicoff, J. B., and Dameshek, W.: Alkaline Phosphatase of Mature Neutrophils in Various "Polycythemias," New England J. Med. **260**:1131, 1959.
Mohler, D. N.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type Associated With Primary Hypogonadism, Am. J. Med. **27**:682, 1959.
Mommaerts, W. F. H. M., and Coauthors: A Functional Disorder of Muscle Associated With the Absence of Phosphorylase, Proc. Nat. Acad. Sc. **45**:791, 1959.

Moore, K. L.: Sex Reversal in Newborn Babies, Lancet **1**:217, 1959.
Moretti, G., and Staeffen, J.: Dysostose cranio-faciale de Crouzon et syringomyélie. Association chez le frère et la soeur, Presse méd. **67**:378, 1959.
Morrison, S. L., and Morris, J. N.: Epidemiological Observations on High Blood-Pressure Without Evident Cause, Lancet **2**:864, 1959.
Morton, N. E.: Genetic Tests Under Incomplete Ascertainment, Am. J. Human Genet. **11**:1, 1959.
Morton, N. E., and Chung, C. S.: Formal Genetics of Muscular Dystrophy, Am. J. Human Genet. **11**:360, 1959.
Mosier, H. D., Scott, L. W., and Cotter, L. M.: The Frequency of the Positive Sex-Chromatin Pattern in Males With Mental Deficiency, Pediatrics **25**:271, 1959.
Motulsky, A. G.: Joseph Adams (1756-1818), a Forgotten Founder of Medical Genetics, A.M.A. Arch. Int. Med. **104**:490, 1959.
Motulsky, A. G., and Gartler, S. M.: Consanguinity and Marriage, Practitioner **183**:170, 1959.
Motulsky, A. G., Kraut, J. M., Thieme, W. T., and Musto, D. F.: Biochemical Genetics of Glucose-6-Phosphate Dehydrogenase Deficiency, Clin. Res. **7**:189, 1959.
Mugler, A.: Un trouble humoral méconnu chez le goutteux: l'hyperoxalémia, Presse méd. **67**:1309, 1959.
Muller, H. J.: The Guidance of Human Evolution, Perspectives Biol. & Med. **3**:1, 1959.
Murayama, M., and Ingram, V. M.: Comparison of Normal Adult Human Haemoglobin With Haemoglobin I by "Fingerprinting," Nature, London **183**:1797, 1959.
Murphy, D. P., and Abbey, H.: Cancer in Families. A Study of the Relatives of 200 Breast Cancer Probands, Cambridge, Mass., 1959, Commonwealth Fund and Harvard University Press.
Murray, J. F.: Pulmonary Disability in the Hurler Syndrome (Lipochondrodystrophy): A Study of Two Cases, New England J. Med. **261**:378, 1959.
Murray, R., Heckel, P., and Hempelmann, L. H.: Leukemia in Children Exposed to Ionizing Radiation, New England J. Med. **261**:585, 1959.
Myers, L. M.: Sex Chromatin in Teratomas, J. Path. & Bact. **78**:43, 1959.
Myerson, R. M., Harrison, E., and Lohmuller, H. W.: Incidence and Significance of Abnormal Hemoglobins. Report of a Series of 1000 Hospitalized Negro Veterans, Am. J. Med. **26**:543, 1959.
Myrianthopoulos, N., and Stevens, H.: Genetic Counseling in Medicine; a New Service for the Community, M. Ann. District of Columbia **28**:256, 1959.

Nachman, M.: The Inheritance of Saccharin Preference, J. Comp. & Physiol. Psychol. **52**:451, 1959.
Naidu, P. M., and Mehdi, Z.: Gonadal Dysgenesis, J. Obst. & Gynec. **66**:122, 1959.
Nalf, R. W., Berry, R. G., and Schlezinger, N. S.: Neurologic Aspects of Porphyria, Neurology **9**:313, 1959.
Nance, W. E.: Twins: An Introduction to Gemellology, Medicine **38**:403, 1959.
Naylor, G. R. E., and Adair, M. E.: Serological Distinction of Adult and Foetal Human Haemoglobin, Nature, London **184**:1854, 1959.
Neel, J. V., Schull, W. J., and Takeshima, K.: A Note on Achondroplasia in Japan, Jap. J. Human Genet. **4**:165, 1959.
Negrelli, B. C.: L'albinisme oculaire lié au sexe dans le cadre du dépistage des hétérozygotes en ophthalmologie, J. génét. humaine, **8**:108, 1959.
Neill, D. W., and Weaver, J. A.: A Study of Some Metabolic Processes Dependent on Coenzyme "A" in Pernicious Anaemia, Acta haemat. **21**:23, 1959.
Newcombe, H. B., Kennedy, J. M., Axford, S. J., and James, A. P.: Automatic Linkage of Vital Records. Computers Can Be Used to Extract "Follow-Up" Statistics of Families From Files of Routine Records, Science **130**:954, 1959.
Nilsson, I. M., Bergman, S., Reitalu, J., and Waldenström, J.: Hemophilia A in a "Girl" With Male Sex-Chromatin Pattern, Lancet **2**:264, 1959.
Nilsson, I. M., Blombäck, M., and Blombäck, B.: Von Willebrand's Disease in Sweden, Its Pathogenesis and Treatment, Acta med. scandinav. **164**:263, 1959.
Nilsson, I. M., Blombäck, M., Thilen, A., and von Francken, I.: Carriers of Hemophilia A, Acta med. scandinav. **165**:357, 1959.
Nishimura, E. T., and Coauthors: Carrier State in Human Acatalasemia, Science **130**:333, 1959.
Noack, M.: Ein Beitrag zum Krankheitsbild der Akrozephalosyndaktylie, Arch. Kinderh. **160**:168, 1959.
Nordmo, S. H.: Blood Groups in Schizophrenia, Alcoholism and Mental Deficiency, Am. J. Psychiat. **116**:460, 1959.
Nour-Eldin, F., and Wilkinson, J. F.: A Congenital Blood-Clotting Anomaly Resembling Coumarin-Induced Defect, Brit. M. J. **1**:1161, 1959.
Nowakowski, H.: Der Hypogonadismus im Knaben- und Mannesalter, Ergebn. inn. Med. Kinderh. **12**:219, 1959.
Nowakowski, H., Lenz, W., and Parada, J.: Diskrepanz zwischen Chromatinbefund und genetischem Geschlecht beim Klinefelter-syndrom, Acta endocrinol. **30**:296, 1959.

VOL. 12 1960

Nugent, C. A., and Tyler, F. H.: The Renal Excretion of Uric Acid in Patients With Gout and Non-Gouty Subjects, J. Clin. Invest. **38**:1890, 1959.
Nyman, M.: Serum Haptoglobin. Methodological and Clinical Studies, Scandinav. J. Clin. & Lab. Invest. **11**:suppl. 39, 1959.

Ober, W. B., Bruno, M. S., Simon, R. M., and Weiner, L.: Hemoglobin S-C Disease With Fat Embolism. Report of a Patient Dying in Crisis: Autopsy Findings, Am. J. Med. **27**:647, 1959.
O'Connell, D.: Heredity in Ankylosing Spondylitis, Ann. Int. Med. **50**:1115, 1959.
Ödman, P.: Hereditary Enchondral Dysostosis, Acta Radiol. **52**:97, 1959.
Ogden, A. L.: Biochemical Polymorphism in Farm Animals, Proc. Roy. Soc. Med. **52**:955, 1959.
Ohno, S., Kaplan, W. D., and Kinosita, R.: Do XY- and O-Sperm Occur in Mus musculus? Exper. Cell. Res. **18**:382, 1959.
Ohno, S., Kaplan, W. D., and Kinosita, R.: On the End-to-End Association of the X and Y Chromosomes of Mus musculus, Exper. Cell Res. **18**:282, 1959.
Ohno, S., Kovacs, E. T., and Kinosita, R.: On the X-Chromosomes of Mouse Mammary Carcinoma Cells, Exper. Cell Res. **16**:462, 1959.
Olmstead, E. G.: Sequential Analysis in the Assignment of Chromosomal Sex by Means of Nuclear Chromatin Patterns in Smears of Oral Mucosa, Am. J. Clin. Path. **32**:346, 1959.
Olsen, M. W.: Fatherless Turkey, J. Am. Vet. M. A. **134**:3, 1959.
Osborne, R. H., Adlersberg, D., De George, F. V., and Wang, C.: Serum Lipids, Heredity and Environment; a Study of Adult Twins, Am. J. Med. **26**:54, 1959.
Osborne, R. H., and DeGeorge, F. V.: A Genetic Component of Variability in Erythrocyte Sedimentation Rate, Am. Naturalist **93**:140, 1959.
Owen, J. A., Mackay, I. R., and Got, C.: Serum Haptoglobins in Hepatobiliary Disease, Brit. M. J. **1**:1454, 1959.
Owen, R. D.: Genetic Aspects of Tissue Transplantation and Tolerance, J. M. Educ. **34**:366, 1959.

Pahwa, J. M., and Singh, L.: Laurence-Moon-Biedl Syndrome—Case Report, Ind. J. M. Sc. **13**:30, 1959.
Paolo, B., Fausto, G., and Efisio, S.: Anemia emolitica acuta da cloramfenicolo in soggetti con anomalie bioenzimatiche eritrocitani, Haematologia **44**:837, 1959.
Parkes, A. S.: Dietary Factors in the Homograft Reaction, Nature, London **184**:699, 1959.
Parkin, D. M.: Blood Groups and Heredity, Practitioner **183**:159, 1959.
Parsons, P. A.: Possible Affinity Between Linkage Groups V and XIII of the House Mouse, Genetica **29**:304, 1959.
Partington, M. W.: An English Family With Waardenburg's Syndrome, Arch. Dis. Childhood **34**:174, 1959.
Paton, D.: Angioid Streaks and Sickle Cell Anemia, A.M.A. Arch. Ophth. **62**:852, 1959.
Patterson, M., and Rios, G.: Muscular Dystrophy in the Gastrointestinal Tract, Texas Rep. Biol. & Med. **17**:502, 1959.
Pender, B.: Islet-Cell Tumor of Pancreas Associated With Peptic Ulceration, Lancet **1**:123, 1959.
Peterson, E. M.: Consideration of Cystic Fibrosis in Adults, With a Study of Sweat Electrolyte Values, J.A.M.A. **171**:87, 1959.
Phillips, J. H., and Burch, G. E.: Cardiovascular Diseases in the White and Negro Races, Am. J. M. Sc. **238**:97, 1959.
Pickering, G. W.: The Nature of Essential Hypertension, Lancet **2**:1027, 1959.
Piguet, B., and Écoiffier, J.: Maladie hémolytique (type Minkowski-Chauffard) et malformations veineuses congénitales, Presse méd. **67**:381, 1959.
Pincus, G., and Coauthors: Effectiveness of an Oral Contraceptive, Science **130**:81, 1959.
Pitney, W. R., and Arnold, B. J.: Plasma Antihaemophilic Factor (AHF) Concentrations in Families of Patients With Haemorrhagic States, Brit. J. Haemat. **5**:184, 1959.
Platt, R.: The Nature of Essential Hypertension, Lancet **2**:55, 1959.
Polani, P. E.: Nuclear Chromatin of Anencephalic Foetuses, Lancet **2**:240, 1959.
Poole, H. K.: The Mitotic Chromosomes of Parthenogenetic and Normal Turkeys, J. Hered. **50**:151, 1959.
Powell, E. D.: Mongolism and Congenital Heart Disease, Irish J. M. Sc. No. 297:40, 1959.
Priest, R. J., and Nixon, R. K.: Familial Recurring Polyserositis: A Disease Entity, Ann. Int. Med. **51**:1253, 1959.
Prins, H. K.: The Separation of Different Types of Human Haemoglobin, J. Chromatog. **2**:445 1959.
Putkonen, T., and Wangel, G. A.: Renal Hyperparathyroidism With Metastatic Calcification of the Skin, Dermatologica **118**:127, 1959.
Pyrah, L. N., Anderson, C. K., Hodgkinson, A., and Lavembeski, P. M.: A Case of Oxalate Nephrocalcinosis and Primary Hyperoxaluria, Brit. J. Urol. **31**:235, 1959.

Quick, A. J.: The Hereditary Hemorrhagic Diseases: Their Classification and Diagnosis, Brit. M. J. **1**:1059, 1959.

Raaschou-Nielsen, W., and Reymann, F.: Familial Benign Chronic Pemphigus, Acta dermat.-venereol. **39**:280, 1959.
Rabson, S. M.: Masters of Modern Pathology: Jakob Erdheim, A.M.A. Arch. Path. **68**:357, 1959.
Rainer, J. D., and Firschein, I. L.: Mating and Fertility Patterns in Families With Early Total Deafness, Eugenics Quart. **6**:117, 1959.
Ramot, B., and Coauthors: Haemoglobin H Disease With Persistent Haemoglobin Bart's in an Oriental Jewess and Her Daughter, Brit. M. J. **2**:1228, 1959.
Ramot, B., and Coauthors: A Study of Subjects With Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency. II. Investigation of Leukocyte Enzymes, J. Clin. Invest. **38**:2234, 1959.
Ramot, B., and Coauthors: A Study of Subjects With Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency. II. Investigation of Platelet Enzymes, J. Clin. Invest. **38**:1659, 1959.
Raper, A. B.: Further Observations on Sickling and Malaria, Tr. Roy. Soc. Trop. Med. & Hyg. **53**:110, 1959.
Rathbun, J. C.: Hypophosphatasia, Helvet. paediat. acta **14**:548, 1959.
Ray, R. N., Cassell, M., and Chaplin, H., Jr.: In Vitro and In Vivo Observations on Stored Sickle Trait Red Blood Cells, Am. J. Clin. Path. **32**:430, 1959.
Raybuck, H. E., and Manter, J. T.: An Anatomical Study of a Case of Clubfoot, Anat. Rec. **133**:677, 1959.
Razis, D. V., Diamond, H. D., and Craver, L. F.: Familial Hodgkin's Disease: Its Significance and Implications, Ann. Int. Med. **51**:933, 1959.
Reed, T. E., and Ahronheim, J. H.: An Association Between ABO Blood Groups and Fertility in a Normal American Population, Nature, London **184**:611, 1959.
Reid, R. T. W.: Marfan's Syndrome Complicated by Dissecting Aneurysm of the Aorta, M. J. Australia **23**:848, 1959.
Renwick, J. H.: Studies of Genetical Linkage in Man, Bull. Johns Hopkins Hosp. **104**:90, 1959.
Rimington, C.: Congenital Porphyria in Animals, Proc. Roy. Soc. Med. **52**:963, 1959.
Rintala, A.: The Histological Appearance of Gastrointestinal Polyps in the Peutz-Jeghers Syndrome, Acta chir. scandinav. **117**:366, 1959.
Roberts, G. B. S.: Fundamental Defects in Fibrocystic Disease of the Pancreas, Lancet **2**:964, 1959.
Roberts, P. D.: Familial Calcification of the Cerebral Basal Ganglia and Its Relation to Hypoparathyroidism, Brain **82**:599, 1959.
Robertson, M. G., and Schroder, J. S.: Pseudoxanthoma Elasticum: A Systemic Disorder, Am. J. Med. **27**:433, 1959.
Robins, M. W.: A Mutation Causing Congenital Clubfoot in the House Mouse, J. Hered. **50**:188, 1959.
Roizin, L., Gold, G., Berman, H. H., and Bonafede, V. I.: Congenital Vascular Anomalies and Their Histopathology in Sturge-Weber-Dimitri Syndrome (Naevus Flammeus With Angiomatosis and Encephalosis Calcificans), J. Neuropath. & Exper. Neurol. **18**:75, 1959.
Roland, C. G.: Klinefelter's Syndrome; Report of a Case With Some Unusual Features, Manitoba M. Rev. **39**:91, 1959.
Roland, C. G., Rogers, A. G., D'Agincourt, R. G.: Multiple Spider Angiomata in a Patient With Klinefelter's Syndrome, Canad. M. A. J. **80**:276, 1959.
Roos, J., and Huizinga, J.: Genetic Investigation of the Stuart Coagulation Defect, Acta genet. **9**:115, 1959.
Rosenfeld, L.: Renal Agenesis (Questions and Answers), J.A.M.A. **170**:1247, 1959.
Rosenoer, V. M., and Franglen, G. T.: Caeruloplasmin in Wilson's Disease, Lancet **2**:1163, 1959.
Rosenthal, D.: Some Factors Associated With Concordance and Discordance With Respect to Schizophrenia in Monozygotic Twins, J. Nerv. & Ment. Dis. **129**:1, 1959.
Ross, L. J.: Congenital Cardiovascular Anomalies in Twins, Circulation **20**:327, 1959.
Ross, R. T.: Multiple and Familial Intracranial Vascular Lesions, Canad. M. A. J. **81**:477, 1959.
Rosse, W. F., and Gurney, C. W.: The Pelger-Huet Anomaly in Three Families and Its Use in Determining the Disappearance of Transfused Neutrophils From the Peripheral Blood, Blood **14**:170, 1959.
Rowen, M. J.: Coarctation of the Aorta in Father and Son, Am. J. Cardiol. **4**:540, 1959.
Rubin, S. I.: A Case of Congenital Amegakaryocytic Thrombocytopenia With Leukemoid Blood Picture and Congenital Deformities, Arch. Pediat. **76**:251, 1959.
Rubini, J. R., Cronkite, C. P., Bond, V. P., and Fliedner, T. M.: Urinary Excretion of Beta Aminoisobutyric Acid (BAIBA) in Irradiated Human Beings, Proc. Soc. Exper. Biol. & Med. **100**:130, 1959.
Rümke, P., and Hellinga, G.: Autoantibodies Against Spermatozoa in Sterile Men, Am. J. Clin. Path. **32**:357, 1959.
Rukavina, J. G., Falls, H. F., Holt, J. F., and Block, W. D.: Léri's Pleonosteosis: A Study of a Family With a Review of the Literature, J. Bone & Joint Surg. **41A**:397, 1959.
Runge, G. H.: Glucose Tolerance in Mongolism, Am. J. Ment. Deficiency **63**:821, 1959.
Rupe, C. O., and Free, A. H.: An Improved Test for Phenylketonuria, Clin. Chem. **5**:405, 1959.
Russell, E. P., and Smith, N. J.: Hereditary Hematuria, A.M.A. J. Dis. Child. **98**:353, 1959.
Russell, W. L., Russell, L. B., and Cupp, M. B.: Dependence of Mutation Frequency on Radiation Dose Rate in Female Mice, Proc. Nat. Acad. Sc. **45**:18, 1959.

VOL. 12 1960

Russell, W. L., Russell, L. B., and Gower, J. S.: Exceptional Inheritance of a Sex-Linked Gene in the Mouse Explained on the Basis that the XO Sex-Chromosome Constitution is Female, Proc. Nat. Acad. Sc. **45**:554, 1959.

Sackner, M. A., Dex, W. J., and Kaplan, A. I.: Sickle Cell–Hemoglobin C Disease and Pregnancy Including a Case of Osteomyelitis, Am. J. Obst. & Gynec. **77**:1328, 1959.
Sacks, M. S., and Coauthors: Isosensitization to a New Blood Factor, Rh^D, With Special Reference to Its Clinical Importance, Ann. Int. Med. **51**:740, 1959.
Saito, T.: A Genetic Study on the Degenerative Anomalies of Deciduous Teeth, Jap. J. Human Genet. **4**:27, 1959.
Salmon, C.: Leucémie aigué et mutations somatiques des substances de groupe sanguin (éditorial), Rev. hémat. **14**:205, 1959.
Salmon, C., André, R., and Dreyfus, B.: Existe-t-il des mutations somatiques du gène de groupe sanguin A au cours de certaines leucémies aigués? Rev. franç. études clin. et biol. **4**:468, 1959.
Sammons, B. P.: Arteriovenous Fistula of the Lung, Radiology **72**:710, 1959.
Sammons, B. P., and Thomas, D. F.: Extensive Lumbar Meningocele Associated With Neurofibromatosis, Am. J. Roentgenol. **81**:1021, 1959.
Sanders, B. E., Miller, O. P., and Richard, M. N.: Preparation of Ceruloplasmin, Arch. Biochem. **84**:60, 1959.
Sandler, L., Hiraizumi, Y., and Sandler, I.: Meiotic Drive in Natural Populations of Drosophila Melanogaster. I. The Cytogenetic Basis of Segregation-Distortion, Genetics **44**:233, 1959.
Sansarricq, H., Marill, G., Portier, A., and Cabannes, R.: Les hémoglobinopathies en Haute-Bolta. Étude statistique, Sang **30**:503, 1959.
Sass-Kortsak, A., Cherniak, M., Geiger, D. W., and Slater, R. J.: Observations on Ceruloplasmin in Wilson's Disease, J. Clin. Invest. **38**:1672, 1959.
Schales, O.: Congenital Hip Dysplasia in Dogs, Vet. Med. **54**:143, 1959.
Schales, O.: Congenital Hip Dysplasia; What We Must Do to Eliminate This Crippling Defect, Popular Dogs, April, 1959, p. 21.
Schappert-Kimmijser, J., Henkes, H. E., and van den Bosch, J.: Amaurosis Congenita (Leber), A.M.A. Arch. Ophth. **61**:211, 1959.
Scheinberg, I. H., and Sternlieb, I.: The Liver in Wilson's Disease, Gastroenterology **37**:550, 1959.
Schenk, V. W. D.: Re-examination of a Family With Pick's Disease, Ann. Human Genet. **23**:325, 1959.
Schiebler, G. L., Adams, P., and Anderson, R. C.: Familial Cardiomegaly in Association With the Wolff-Parkinson-White Syndrome, Am. Heart J. **58**:113, 1959.
Schiff, L., Billing, B. H., and Oikawa, Y.: Familial Nonhemolytic Jaundice With Conjugated Bilirubin in the Serum; a Case Study, New England J. Med. **260**:1315, 1959.
Schmid, R.: Jaundice and Bilirubin Metabolism, Bull. New York Acad. Med. **35**:755, 1959.
Schmid, R., and Hammaker, L.: Glucuronide Formation in Patients With Constitutional Hepatic Dysfunction (Gilbert's Disease), New England J. Med. **260**:1310, 1959.
Schmid, R., and Mahler, R.: Chronic Progressive Myopathy With Myoglobinuria: Demonstration of a Glycogenolytic Defect in the Muscle, J. Clin. Invest. **38**:2044, 1959.
Schmid, R., Robbins, P. W., and Traut, R. R.: Glycogen Synthesis in Muscle Lacking Phosphorylase, Proc. Nat. Acad. Sc. **45**:1236, 1959.
Schmidt, R., Brecher, G., and Clemens, T.: Familial Hemolytic Anemia With Erythrocyte Inclusion Bodies and a Defect in Pigment Metabolism, Blood **14**:991, 1959.
Schneeberg, N. G., and Coauthors: Congenital Virilizing Adrenal Hyperplasia in Identical Twins, J. Clin. Endocrinol. **19**:203, 1959.
Schneider, R. G., and Haggard, M. E.: A New Haemoglobin Variant in an American Negro, Brit. M. J. **2**:285, 1959.
Schnelle, G. B.: Canine Hip Dysplasia, Lab. Invest. **8**:1178, 1959.
Schnelle, G. B.: Congenital Dysplasia of the Hip in Dogs (Editorial), J. Am. Vet. M. A. **135**:235, 1959.
Schoen, E. J.: "Lowe's Syndrome." Abnormalities in Renal Tubular Function in Combination With Other Congenital Defects, Am. J. Med. **27**:781, 1959.
Schreier, K.: Die nichtdiabetischen Melliturien, Ergebn. inn. Med. Kinderh. **12**:493, 1959.
Schreier, S. L., and Coauthors: The Hemolytic Effect of Primaquine. X. Aldolase and Glyceraldehyde-3-Phosphate Dehydrogenase Activity in Primaquine-Sensitive Erythrocytes, J. Lab. & Clin. Med. **54**:232, 1959.
Schull, W. J.: Consanguinity and the Etiology of Congenital Malformations, Pediatrics **23**:195, 1959.
Schull, W. J.: A Geneticist Looks at the Radiation Hazard, Radiology **72**:522, 1959.
Schultz, J.: Antigens and Antibodies as Cell Phenotypes, Science **129**:937, 1959.
Schwartz, S.: Unsuspected Osteochondrodystrophy (Morquio's Disease), Arth. & Rheum. **2**:559, 1959.
Scott, W. G., and Evans, T., editors: Genetics, Radiobiology and Radiology. Proceedings, Mid-Western Conference, Springfield, Ill., 1959, Charles C Thomas, Publisher.
Scowen, E. F., Stansfeld, A. G., and Watts, R. E.: Oxalosis and Primary Hyperoxaluria, J. Path. & Bact. **77**:195, 1959.

Searle, A. G.: Hereditary Absence of the Spleen in the Mouse, Nature, London **184**:1419, 1959.
Searle, A. G.: The Incidence of Anencephaly in a Polytypic Population, Ann. Human Genet. **23**:279, 1959.
Segar, W. E.: Idiopathic Paroxysmal Myoglobinuria, Pediatrics **23**:12, 1959.
Seltzer, C. C.: Masculinity and Smoking, Science **130**:1706, 1959.
Seman, G.: Sur une anomalie constitutionnelle héréditaire du noyau des polynucléaires neutrophiles, Rev. hémat. **14**:409, 1959.
Serra, J. A.: A Position-Effect Explanation of Gene Conversion, Nature, London **183**:700, 1959.
Seven, M. J., Kliman, B., and Peterson, R. E.: Clinical Studies With Penicillamine in Hepatolenticular Degeneration, Am. J. M. Sc. **237**:49, 1959.
Shahidi, N. T., and Diamond, L. K.: Enzyme Deficiency in Erythrocytes in Congenital Nonspherocytic Hemolytic Anemia, Pediatrics **24**:245, 1959.
Sharpe, A. R., Jr., Fox, P. G., Jr., and Dodson, A. I., Sr.: Unilateral Renal Haematuria Associated With Sickle Cell C Disease and Sickle Cell Trait: Study of Five Patients and Review of Literature, J. Urol. **81**:780, 1959.
Shaw, S., and Oliver, R. A. M.: Congenital Hypoplastic Thrombocytopenia With Skeletal Deformities in Siblings, Blood **14**:374, 1959.
Sheldon, W., and Blackton, K. D.: Coeliac Disease, Pediatrics **23**:132, 1959.
Shepard, T. H., Landing, B. H., and Mason, D. C.: Familial Addison's Disease. Case Reports of Two Sisters With Corticoid Deficiency Unassociated With Hypoaldosteronism, A.M.A. J. Dis. Child. **97**:154, 1959.
Shiller, J. G.: Craniofacial Dysostosis of Crouzon; a Case Report and Pedigree With Emphasis on Heredity, Pediatrics **23**:107, 1959.
Siekert, R. G., Keith, H. M., and Dion, F. R.: Ataxia-Telangiectasia in Children, Proc. Staff Meet. Mayo Clin. **34**:581, 1959.
Sievers, M. L.: Hereditary Aspects of Gastric Secretory Function, Am. J. Med. **27**:246, 1959.
Silber, R., and Christensen, W. R.: Pseudotumor of Hemophilia in a Patient With PTC Deficiency, Blood **14**:585, 1959.
Silvestroni, E.: Emoglobine abnormi ed emoglobinopatie in Italia, Policlinico **66**:1373, 1959.
Silvestroni, E., Bianco, I., and Muzzolini, M.: Type D Hemoglobin in an Italian Family of Calabrian Origin, Policlinico **66**:41, 1959.
Simpson, D. A., Lander, H., and Robson, H. N.: Observations on Kuru. II. Clinical Features, Austral. Ann. Med. **8**:8, 1959.
Singer, R.: The Coronary Arteries of the Bantu Heart, South African M. J. **1**:310, 1959.
Singer, S. J., and Itano, H. A.: On the Asymmetrical Dissociation of Human Hemoglobin, Proc. Nat. Acad. Sc. **45**:174, 1959.
Sinsheimer, R. L.: Is the Nucleic Acid Message in a Two-Symbol Code? J. Mol. Biol. **1**:218, 1959
Siskind, G. W., and Thomas, L.: Studies on the Runting Syndrome in Newborn Mice, J. Exper. Med. **110**:511, 1959.
Slavin, H. B., Alling, E. L., and Keutmann, E. H.: Agammaglobulinemia: Report of a Case of Historical Interest, New England J. Med. **260**:852, 1959.
Smith, C. A. B.: A Note on the Effects of Method of Ascertainment on Segregation Ratios, Ann. Human Genet. **23**:311, 1959.
Smith, C. A. B.: Some Comments on the Statistical Methods Used in Linkage Investigations, Am. J. Human Genet. **11**:289, 1959.
Smith, D. R., Kolb, F. O., and Harper, H. A.: The Management of Cystinuria and Cystine-Stone Disease, J. Urol. **81**:61, 1959.
Smith, E. W., and Conley, C. L.: Sickle Cell–Hemoglobin D Disease, Ann. Int. Med. **50**:94, 1959.
Smith, E. W., and Krevans, J. R.: Clinical Manifestations of Hemoglobin C Disorders, Bull. Johns Hopkins Hosp. **104**:17, 1959.
Smith, J. L., and Cogan, D. G.: Ataxia-Telangiectasia, A.M.A. Arch. Ophth. **62**:364, 1959.
Smith, J. M.: A Theory of Aging, Nature, London **184**:956, 1959.
Smith, W. G.: Desmoid Tumors in Familial Multiple Polyposis, Proc. Staff Meet. Mayo Clin. **34**:31, 1959.
Smithies, O.: An Improved Procedure for Starch-Gel Electrophoresis: Further Variations in the Serum Proteins of Normal Individuals, Biochem. J. **71**:585, 1959.
Smithies, O., and Hiller, O.: The Genetic Control of Transferrins in Humans, Biochem. J. **72**:121, 1959.
Smoller, M., and Hsia, D. Y.-Y.: Studies on the Genetic Mechanism of Cystic Fibrosis of the Pancreas, A.M.A. J. Dis. Child. **98**:277, 1959.
Snavely, J. G.: The Genetic Aspects of Hip Dysplasia in Dogs., J. Am. Vet. M. A. **135**:201, 1959.
Snyder, L. H.: Fifty Years of Medical Genetics, Science **129**:7, 1959.
Sokal, G., Verstraete, M., and Vermylen, C.: Diathèse hémorrhagique familiale par déficience qualitative des plaquettes sanguines, Acta haemat. **22**:165, 1959.
Sorensen, L. B.: Degradation of Uric Acid in Man, Metabolism **8**:687, 1959.
Sorsby, A.: Principles of Heredity, Practitioner **183**:133, 1959.
Spain, D. M., and Nathan, D. J.: Body Form, Urinary Estrogens, Serum Cholesterol and Coronary Artery Disease in Adult White Males, Am. J. M. Sc. **238**:584, 1959.

VOL.
12
1960

Sporn, M. B., Dingman, W., Defalco, A., and Davies, R. K.: Formation of Urea from Arginine in the Brain of the Living Rat, Nature, London **183**:1520, 1959.
Spurling, C. L., and Sacks, M. S.: Inherited Hemorrhagic Disorder With Antihemophilic Globulin Deficiency and Prolonged Bleeding Time (Vascular Hemophilia), New England J. Med. **261**:311, 1959.
Srivastava, B. N., Gupta, M. L., and Singh, S.: Bourneville's Disease; Report of a Case With Brief Review of Literature, Indian J. M. Sc. **13**:34, 1959.
Stadler, S. R.: The Relationship of Gene Conversion to Crossing Over in Neurospora, Proc. Nat. Acad. Sc. **45**:1625, 1959.
Steen, R. E.: Hunter's Polydystrophy (Gargoylism) With Cardiac Lesions and Some Formes Frustes, Brit. Heart J. **21**:269, 1959.
Steinbach, M., and Pejaudier, L.: The Behavior of Haptoglobin During Routine Fractionation, Nature, London **184**:362, 1959.
Steinberg, A. G.: Detection of Sex-Reversed Human Beings, Science **129**:403, 1959.
Steinberg, A. G.: Methodology in Human Genetics, J. M. Educ. **34**:315, 1959.
Steinberg, A. G., and Giles, B. D.: A Genetically Determined Human Serum Factor Detected by Its Effect on a Mating Reaction in Yeast, Am. J. Human Genet. **11**:380, 1959.
Steinberg, S. H., Steinberg, A. J., and Steinberg, G. J.: Cleidocranial Dysostosis; Report of Three Cases in One Family, M. Ann. District of Columbia **28**:16, 1959.
Steiner, M. M.: Modern Concepts of Urologic Endocrinology, J. Urol. **81**:1, 1959.
Stenstedt, Å.: Involutional Melancholia: an Etiologic, Clinical, and Social Study of Endogenous Depression in Later Life With Special Reference to Genetic Factors, Copenhagen, 1959, Ejnar Munksgaards Forlag.
Stephens, F. E., and Isaacson, A.: Hereditary Multiple Lipomatosis, J. Hered. **50**:51, 1959.
Stern, C.: The Chromosomes of Man, J. M. Educ. **34**:301, 1959.
Stern, C.: Colour-Blindness in Klinefelter's Syndrome, Nature, London **183**:1452, 1959.
Stern, C.: Use of the Term "Superfemale," Lancet **2**:1088, 1959.
Stetten, D., Jr.: Gout, Perspectives Biol. & Med. **2**:185, 1959.
Stevanović, D. V.: Alopecia Congenita, Acta genet. **9**:127, 1959.
Stevens, L. C., Mackensen, J. A., and Bernstein, S. E.: A Mutation Causing Neonatal Jaundice in the House Mouse, J. Hered. **50**:35, 1959.
Stevenson, A. C.: Observations on the Results of Pregnancies in Women Resident in Belfast. III. Sex Ratio With Particular Reference to Nuclear Sexing of Chorionic Villi of Abortions, Ann. Human Genet. **23**:415, 1959.
Stevenson, A. C., Dudgeon, M. Y., and McClure, H. I.: Observations on the Results of Pregnancies in Women Resident in Belfast. II. Abortions, Hydatidiform Moles and Ectopic Pregnancies, Ann. Human Genet. **23**:395, 1959.
Stevenson, A. C., and Warnock, H. A.: Observations on the Results of Pregnancies in Women Resident in Belfast. I. Data Relating to All Pregnancies Ending in 1957, Ann. Human Genet. **23**:382, 1959.
Stewart, J. S. S.: Genetic Factors in Intersexes, Proc. Roy. Soc. Med. **52**:817, 1959.
Stewart, J. S. S.: Medullary Gonadal Dysgenesis (Chromatin-Positive Klinefelter's Syndrome). A Genetically Determined Condition With Eunuchoid Measurements but Early Epiphyseal Closure, Lancet **1**:1175, 1959.
Stewart, J. S. S.: Testicular Feminisation and Colour-Blindness, Lancet **2**:592, 1959.
Stewart, R. N.: Anomalies of Form and Function in Friedreich's Ataxia, Scot. M. J. **4**:84, 1959.
Stich, M. H.: Carbazochrome Salicylate Therapy in Hereditary Hemorrhagic Telangiectasia, New York J. Med. **59**:2725, 1959.
Stocker, B. A. D.: Bacterial Genetics and Infectious Disease. J. M. Educ. **34**:354, 1959.
Stool, N., Sullivan, C. R., and Bigelow, C. E.: Osteogenesis Imperfecta in a 95-Year-Old Woman, Proc. Staff Meet. Mayo Clin. **34**:523, 1959.
Streete, B. G., and Stull, F. E., Jr.: Kartagener's Syndrome, A.M.A. Arch. Surg. **79**:156, 1959.
Suarey, R. M., Buso, R., Meyer, L. M., and Olovamietta, S. T.: Distribution of Abnormal Hemoglobins in Puerto Rico and Survival Studies of Red Blood Cells Using Cr^{51}, Blood **14**:255, 1959.
Sukumaran, P. K., Sanghvi, L. D., Ager, J. A. M., and Lehmann, H.: Haemoglobin L in Bombay: Findings in Three Gujarati Speaking Lohana Families, Acta genet. **9**:202, 1959.
Sussman, L., Meyer, L. H., and Conrad, R. A.: Blood Groupings in Marshallese, Science **129**:644, 1959.
Sutton, H. E., and Coauthors: The Frequencies of Haptoglobin Types in Five Populations, Ann. Human Genet. **23**:175, 1959.
Sutton, P. R. N.: Association Between Colour of the Iris of the Eye and Reaction to Dental Pain, Nature, London **184**:122, 1959.
Swain, J. M.: Electroencephalographic Abnormalities in Presenile Atrophy, Neurology **9**:722, 1959.
Swanton, M. C.: Hemophilic Athropathy in Dogs, Lab. Invest. **8**:1269, 1959.
Swenson, O.: Hirschsprung's Disease (Aganglionic Megacolon), New England J. Med. **260**:972, 1959.

Swenson, O., Fisher, J. H., and Gherardi, G. J.: Rectal Biopsy in the Diagnosis of Hirschsprung's Disease, Surgery **45**:690, 1959.
Szilard, L.: On the Nature of the Aging Process, Proc. Nat. Acad. Sc. **45**:30, 1959.
Szilard, L.: A Theory of Aging, Nature, London **184**:957, 1959.

Takahashi, T.: Clinical Study on the Systemic Disorders With Congenital Disturbance of Enchondral Ossification, Especially Chondrodystrophia Fetalis and Chondro-osteodystrophy, Jap. J. Human Genet. **4**:55, 1959.
Tamura, A., Takahashi, M., Ishii, H., and Akashi, S.: A Study on the Hereditary Black Blood Disease (Tamura and Takahashi's Disease or Nigremia Hereditaria), Jap. J. Human Genet. **4**:180, 1959.
Tanner, J. M., Healy, M. J. R., Whitehouse, R. H., and Edgson, A. C.: The Relation of Body Build to the Excretion of 17-Ketosteroids and 17-Ketogenic Steroids in Healthy Young Men, J. Endocrinol. **19**:87, 1959.
Tanner, J. M., Prader, A., Habich, M., Ferguson-Smith, M. A.: Genes on the Y Chromosome Influencing Rate of Maturation in Man, Lancet **2**:141, 1959.
Tatarsky, J., Stroup, M., Levine, P., and Ernoehazy, W. S.: Another Example of Anti-Diego (Di^a), Vox Sang. **4**:152, 1959.
Taylor, W. J., Jackson, F. C., and Jensen, W. N.: Wilson's Disease, Portal Hypertension and Intrahepatic Vascular Obstruction, New England J. Med. **260**:1160, 1959.
Thomas, C. B.: Familial Patterns in Hypertension and Coronary Heart Disease, Circulation **20**:25, 1959.
Thomas, L.: Future Lines of Research on Rheumatoid Arthritis, J. CHRON. DIS. **10**:428, 1959.
Thomas, L., Douglas, G. W., and Carr, M. C.: The Continual Migration of Syncytial Trophoblasts From the Fetal Placenta Into the Maternal Circulation, Tr. A. Am. Physicians **72**:140, 1959.
Thompson, M. M., Jr.: Anencephaly in One Twin; a Case Report, Ohio M. J. **55**:353, 1959.
Thompson, M. W.: A New Heredity Counseling Service in Western Canada, Eugenics Quart. **6**:167, 1959.
Thompson, N.: Cherubism: Familial Fibrous Dysplasia of the Jaws, Brit. J. Plast. Surg. **12**:89, 1959.
Thomsen, N. J.: Macrocytic Anemia of Pregnancy and Pernicious Anemia in Relatives, Acta med. scandinav. **165**:29, 1959.
Thorén, C.: Cardiopathy in Friedreich's Ataxia, Acta paediat. suppl. 118, 1959.
Tjio, J. H., Puck, T. T., and Robinson, A.: The Somatic Chromosomal Constitution of Some Human Subjects With Genetic Defects, Proc. Nat. Acad. Sc. **45**:1008, 1959.
Törnblom, N., Malers, E., and Wallenius, G.: Osteodermatopathia Hypertrophicans, Acta med. scandinav. **164**:325, 1959.
Toller, P. A.: Clinical Report on 6 Cases of Amelogenesis Imperfecta, Oral Surg. **12**:325, 1959.
Touster, O.: Pentose Metabolism and Pentosuria, Am. J. Med. **26**:724, 1959.
Towner, C. H.: Familial Incidence of Henoch-Schönlein Syndrome, Brit. M. J. **2**:1385, 1959.
Tuchinda, S., Vareenil, C., Bhanchit, P., and Minnich, V.: "Fast" Hemoglobin Component Found in Umbilical Cord Blood of Thai Babies, Pediatrics **24**:43, 1959.
Tuchman, L. R., Goldstein, G., and Clyman, M.: Studies on the Nature of the Increased Serum Acid Phosphatase in Gaucher's Disease, Am. J. Med. **27**:959, 1959.
Tuna, N.: Aneurysmal Venous Dilatation in Marfan's Syndrome, Dis. Chest **36**:204, 1959.
Turpin, R., Lejeune, J., Lafourcade, J., and Gautier, M.: Aberrations chromosomiques et maladies humaines. La polydysspondylie à 45 chromosomes, C. rend. Acad. sc. **248**:3636, 1959.

Ueno, S., Matzuzawa, S., Kitamura, S., and Mishima, H.: Blood Group Studies on the Antigenic Structure of Human Red Cells and Its Relation to the So-Called Secretor and Non-secretor With Special Reference to Its Heredity, J. Immunol. **82**:385, 1959.
Ueno, S., Suzuki, K., and Yamazawa, K.: Human Chimerism in a Pair of Twins, Acta genet. **8**:47, 1959.

Vacca, J. B., Knight, W. A., and Broun, G. O.: Clinical Observations Regarding Xanthelasma, Ann. Int. Med. **51**:1019, 1959.
Van Arsdel, P. P., Jr., and Motulsky, A. G.: Blood Groups and Secretion of Blood Group Substances; Comparison of Allergic With Non-allergic Persons in a Pacific Northwest College Population, J. Allergy **30**:460, 1959.
Van Arsdel, P. P., Jr., and Motulsky, A. G.: Frequency and Heritability of Asthma and Allergic Rhinitis in College Students, Acta genet. **9**:101, 1959.
van Buchem, F. S. P.: Arachnodactyly Heart, Circulation **20**:88, 1959.
van Buchem, F. S. P., Arends, A., and Schröder, E. A.: Endocardial Fibroelastosis in Adolescents and Adults, Brit. Heart J. **11**:229, 1959.
van den Bosch, J.: Microcephaly in the Netherlands; a Clinical and Genetic Study, Ann. Human Genet. **23**:91, 1959.

VOL. 12 1960

van der Hoog, C. E.: Ataxia Teleangiectatica, Maandschr. kindergeneesk. **27**:26, 1959.
Van Dijk, M. C.: Two Cases of Thalassaemia With Haemoglobin E, Trop. & Geog. Med. **11**:96, 1959.
van Geffel, R., and Coauthors: Galactosemia: Genetic Considerations, Arch. franç. pédiat. **16**:158, 1959.
van Loghem, J. J., Jr., Dorfmeijer, H., van der Hart, M., and Schreuder, F.: Serological and Genetic Studies on a Platelet Antigen (Zw), Vox Sang. **4**:161, 1959.
Vella, F.: Heterogeneity of Human Foetal Haemoglobin: Incidence of Foetal Variants in Singapore, Nature, London **184**:272, 1959.
Vella, F., Ager, J. A., and Lehmann, H.: New Variant of Human Foetal Haemoglobin, Nature, London **183**:31, 1959.
Versé, H.: Das "Marfan-Syndrom" (Dystrophia mesodermalis congenita Typ Marfan; Arachnodaktylie), Ergebn. inn. Med. Kinderh. **11**:141, 1959.
Vinograd, J. R., Hutchinson, W. D., and Schroeder, W. R.: C^{14}-hybrids of Human Hemoglobins. II. The Identification of the Aberrant Chain in Human Hemoglobin S, J. Am. Chem. Soc. **81**:3168, 1959.
Vlahakis, G., and Heston, W. E.: Relationship Between Recessive Obesity and Induced Pulmonary Tumors in Mice, J. Hered. **50**:99, 1959.
Vogel, F.: Moderne Probleme der Humangenetik, Ergebn. inn. Med. Kinderh. **12**:52, 1959.
Vogel, F., and Götze, W.: Familienuntersuchungen zur Genetik des normalen Elektrencephalogramms, Deutsche Ztschr. Nervenh. **178**:668, 1959.
Vogel, F., and Hembold, W.: Koppelungsdaten für zwei wahrscheinlich einfach mendelnde EEG-Merkmale des Menschen, Ztschr. menschl. Vererb.- u. Konstitutionslehre **35**:28, 1959.
Voridis, E., and Maurice, P.: Familial Cardiomegaly, Arch. mal. coeur **52**:1410, 1959.

Walford, R. L., and Schneider, R.: Serum Elastase Inhibitor. Levels in Animal and Human Sera, Including Selected Disease States, Proc. Soc. Exper. Biol. & Med. **101**:31, 1959.
Walker, D. G., and Bowman, J. E.: Glutathione Stability of the Erythrocytes in Iranians, Nature, London **184**:132S, 1959.
Wallace, M. E.: An Experimental Test of the Hypothesis of Affinity, Genetica **29**:243, 1959.
Walls, G. L., and Heath, G. G.: Dominant Ectopia Lentis et Pupillae, Am. J. Human Genet. **11**:166, 1959.
Walls, W. L., Altman, D. H., and Winslow, O.: Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome), A.M.A. J. Dis. Child. **98**:242, 1959.
Walsh, F. B., and Hoyt, W. F.: External Ophthalmoplegia: As Part of Congenital Myasthenia in Siblings: Myasthenia Gravis in Children: Report of a Family Showing Congenital Myasthenia, Am. J. Ophth. **47**:28, 1959.
Walshe, J. M.: Current Views on the Pathogenesis and Treatment of Wilson's Disease, Arch. Int. Med. **103**:155, 1959.
Wansbrough, R. M., Carrie, A. W., Walker, N. F., and Ruckerbauer, G.: Coxa Plana, Its Genetic Aspects and Results of Treatment With Long-Taylor Walking Caliper, J. Bone & Joint Surg. **41A**:135, 1959.
Ward, J. A., Haltiwanger, E., Jr., and King, R. E.: Pseudorenal Glycosuria and Polycystic Kidney Disease, J. Urol. **82**:449, 1959.
Warkany, J., Beaudry, P. H., and Hornstein, S.: Attempted Abortion With Aminopterin (4-aminopteroylglutamic acid); Malformations of the Child, A.M.A. J. Dis. Child. **97**:274, 1959.
Warwick, W. J., Holman, R. T., Quie, P. G., and Good, R. A.: Chylous Ascites and Lymphedema, A.M.A. J. Dis. Child. **98**:317, 1959.
Watkins, W. M., and Morgan, W. T. J.: Possible Genetic Pathways for Biosynthesis of Blood Group Mucopolysaccharides, Vox Sang. **4**:97, 1959.
Watson, C. J., and Coauthors: Some Studies of the Comparative Biology of Human and Bovine Erythropoietic Porphyria, A.M.A. Arch. Int. Med. **103**:436, 1959.
Way, S., Hetherington, J., and Galloway, D. C.: Simultaneous Cytological Diagnosis of Cervical Cancer in Three Sisters, Lancet **2**:890, 1959.
Weaver, W. F., Edwards, J. E., and Brandenburg, R. O.: Idiopathic Dilatation of the Aorta With Aortic Valvular Insufficiency: A Possible Forme Fruste of Marfan's Syndrome, Proc. Staff Meet. Mayo Clin. **34**:518, 1959.
Weijers, H. A., and van de Kamer, J. H.: Coeliac Disease. VII. Application and Interpretation of the Gliadine Tolerance Curve, Acta paediat. **48**:17, 1959.
Weil, A. J., and Finkler, A. E.: Isoantigenicity of Rabbit Semen, Proc. Soc. Exper. Biol. & Med. **102**:624, 1959.
Welshons, W. J., and Russell, L. B.: The Y Chromosome as the Bearer of Male Determining Factors in the Mouse, Proc. Nat. Acad. Sc. **45**:560, 1959.
Welford, N. T.: Facial Paralysis Associated With Osteopetrosis (Marble Bones), J. Pediat. **55**:67, 1959.
Welter, H.-T.: Einer bisher unbekannte hereditäre Hepatosplenomegalie mit hämorrhagischer Diathese, Folia haemat. **3**:117, 1959.
Wendt, G. G. von, Landzettel, H. J., and Unterreiner, I.: Das Erkrankungsalter bei der Huntingtonschen Chorea, Acta genet. **9**:18, 1959.

L.
2
60

Went, L. N., and MacIver, J. E.: Sickle-Cell/Haemoglobin-J Disease, Brit. M. J. **2**:138, 1959.
Wheelen, L., and Race, R. R.: Familial Alzheimer's Disease; With a Note on the Linkage Data, Ann. Human Genet. **23**:300, 1959.
White, C., and Eisenberg, H.: ABO Blood Groups and Stomach Cancer, Yale J. Biol. & Med. **32**:58, 1959.
Wiener, A. S.: Application of Blood Grouping Tests in Cases of Disputed Maternity, J. Forensic Sc. **4**:351, 1959.
Wiener, A. S., and Unger, L. J.: Rh Factors Related to the Rh_o Factor as a Source of Clinical Problems, J.A.M.A. **169**:696, 1959.
Wilkins, R. W., and Sommers, S. C.: Enlargement of the Heart, Cardiac Failure, and Loose, Dry, Scaly Skin, Am. J. Clin. Path. **31**:66, 1959.
Williams, R. S.: Increased Thyroid Function in Haemochromatosis, Brit. M. J. **1**:1078, 1959.
Winer, J. H.: Practical Value of Analysis of Urinary Calculi, J.A.M.A. **169**:1715, 1959.
Wise, D., and Carter, C. O.: Osteochondrodystrophy, Lancet **2**:566, 1959.
Wohlwill, F. J., Bernstein, J., and Yakovlev, P. I.: Dysmyelinogenic Leukodystrophy; Report of a Case of a New, Presumably Familial Type of Leukodystrophy With Megalobarencephaly, J. Neuropath. & Exper. Neurol. **18**:359, 1959.
Wolfe, H. G.: Blood-pH Differences in Two Inbred Strains of Mice, J. Hered. **50**:155, 1959.
Wood, J. A., and Coauthors: A Comparison of Sweat Chlorides and Intestinal Fat Absorption in Chronic Obstructive Pulmonary Emphysema and Fibrocystic Disease of the Pancreas, New England J. Med. **260**:951, 1959.
Woodruff, M. F. A., and Lennox, B.: Reciprocal Skin Grafts in a Pair of Twins Showing Blood Chimaerism, Lancet **2**:476, 1959.
Woodworth, J. A., Beckett, R. S., and Netsky, M. G.: A Composite of Hereditary Ataxias, A.M.A. Arch. Int. Med. **104**:594, 1959.
Worthen, H. G., Vernier, R. L., and Good, R. A.: Infantile Nephrosis, A.M.A. J. Dis. Child. **98**:731, 1959.
Wortis, J., and Giancotti, A. M.: A New Simple Test Paper for Mass Detection of Phenylketonuria, Am. J. Pub. Health **49**:463, 1959.
Wright, I. S.: Concerning the Functions and Nomenclature of Blood Clotting Factors, With a Preliminary Report of the Profile of Blood Clotting Factors in Young Males, Ann. Int. Med. **51**:841, 1959.
Wright, I. S., Chairman, International Committee: Nomenclature of Blood Clotting Factors, Canad. M.A.J. **80**:659, 1959.
Wright, I. S. (for International Committee): Nomenclature of Blood Clotting Factors. Four Factors, Their Characterization and International Number, J.A.M.A. **170**:325, 1959.
Wright, S.: Genetics and the Hierarchy of Biological Sciences, Science **130**:959, 1959.
Wright, S.: Physiological Genetics, Ecology of Populations, and Natural Selection, Perspectives Biol. & Med. **3**:107, 1959.
Wright, S. W., Tarjan, G., and Eyer, L.: Investigation of Families With Two or More Mentally Defective Siblings: Clinical Observations, A.M.A. J. Dis. Child. **97**:445, 1959.
Wuhrmann, F.: Double Albumin Peaks as an Hereditary Blood Protein Anomaly, Schweiz. med. Wchnschr. **89**:150, 1959.

Yamamoto, T.: A Further Study on Induction of Functional Sex Reversal in Genotypic Males of the Medaka (Oryzias latipes) and Progenies of Sex Reversals, Genetics **44**:739, 1959.
Yoss, R. E., and Daly, D. O.: Treatment of Narcolepsy With Ritalin, Neurology **9**:171, 1959.

Zaidi, Z. H.: Ehlers-Danlos Syndrome With Congenital Herniae and Pigeon Breast, Brit. M. J. **2**:175, 1959.
Zak, S. J., and Good, R.: Immunochemical Studies of Human Serum Gamma Globulins, J. Clin. Invest. **38**:579, 1959.
Zanchi, M.: Rilievi morfologici e istochimici su due casi sporadici di controdistrofia, Folia hered. et. path. **8**:389, 1959.
Zegarelli, E. V., and Coauthors: Atlas of Oral Lesions Observed in the Syndrome of Oral Melanosis With Associated Intestinal Polyposis (Peutz-Jeghers Syndrome), Am. J. Digest. Dis. **4**:479, 1959.
Zellweger, H., and Bell, S. E.: Congenital Muscular Hypertrophy, Neurology **9**:160, 1959.
Zeman, W., Kaeibling, R., and Pasamanick, B.: Idiopathic Dystonia Musculorum Deformans. I. The Hereditary Pattern, Am. J. Human Genet. **11**:188, 1959.
Zinkham, W. H.: Glutathione Metabolism, Pediatrics **23**:18, 1959.
Zinkham, W. H., and Lenhard, R. E., Jr.: Metabolic Abnormalities of Erythrocytes From Patients With Congenital Nonspherocytic Hemolytic Anemia, J. Pediat. **55**:319, 1959.
Zöllner, N.: Inborn Disorders of Metabolism, J. CHRON. DIS. **10**:6, 1959.

VOL. 12 1960